Molecular mechanisms, symptoms and treatments in cystic fibrosis

Health & Medicine, Disease

Introduction

Cystic fibrosis is a genetic disorder currently affecting over 9000 people living in the United Kingdom alone, with millions of people carrying the faulty recessive gene responsible for the disease. This essay is split into 4 distinct sections, firstly looking at the faulty gene and its effects on the organs of the body, followed by an in-depth look at the symptoms of patients suffering with cystic fibrosis, whereas the third section will look at the treatments available to sufferers. The forth section will contain potential future cures and treatments for the cystic fibrosis.

Molecular Mechanisms

The faulty gene that codes for cystic fibrosis affects organs such as the lungs and pancreas. This fault causes high mucosal build up in these organs. Noticeably with regards to the lungs as the high volume of mucous can cause severe breathing difficulties.

The cystic fibrosis transmembrane regulator (CFTR) protein is coded for by the CFTR gene, in chromosome 7 of the human genome. CFTR is a glycoprotein made up of 1480 amino acids consisting of 5 domains. The CFTR protein is responsible for a variety of functions in the apical membranes of cells including the transport of chloride ions, regulation of the sodium ion channels and the regulation of hydrogen carbonate ion transport across the apical membrane[3]. However, it seems that the main contributing factor to cystic fibrosis is the transportation of chloride ions across the apical membrane and sodium ion regulation.

Mutations in the CFTR gene can be categorized into 6 classes; depending on the effect they have on the production of the CFTR protein. The mutations are listed below in Figure 1, with the consequence of the mutation on the CFTR protein.

Mutation Number	Consequence of Mutation
I	Not synthesised
II	Inadequately processed
III	Not regulated
IV	Shows abnormal conductance
V	Partially defective production
VI	Accelerated degradation

Figure 1 – Table showing the Mutation Number and the Consequence of the mutation on the CFTR protein

The mutations stated in figure 1, either cause the CFTR protein to become ineffective or prevents synthesis altogether. Classes I and III prevent synthesis of the CFTR protein, whereas other mutations cause problems in the production of the protein. Class II mutations effects can vary from the CFTR protein being completely dysfunctional to significantly reduced function depending on the patient. Class IV and Class V mutations do not cause the CFTR protein to cease working, but do have a derogatory effect on their function. Class VI mutations cause before-time degradation of the protein meaning reduced function.

One of the consequences of the CFTR protein not functioning in cystic fibrosis patients is a high concentration of chloride ions developing in the intracellular space, as well as little regulation of sodium ions entering the cell. Under normal circumstances water would diffuse out the cell and contribute to the airway surface liquid as the concentrations of chloride and sodium ions would be higher in the extracellular space. However with a defective CFTR gene the osmotic gradient is reversed. Thus leading to a high ion concentration within the cell and depletion in the airway surface liquid.

Cilia are small hair like projections in the respiratory tract which are responsible for wafting the mucous up the respiratory tract so it can be swallowed and infection averted. Mucous is one of the body’s primary physical defences against bacterial infection. Pathogens capable of causing respiratory disease are caught on the mucous in the respiratory tract and eventually swallowed with the aid of cilia thus avoiding the entry of pathogens into the lungs and causing bacterial infection. Airway surface liquid also prevents infection by facilitating the movement of mucous up the respiratory tract. However when there is depletion in airway surface liquid, the cilia are also affected. The mucous therefore needs to be of low viscosity so it can be easily moved up the respiratory tract. However, due to the lack of airway surface liquid in a patient with cystic fibrosis the mucous becomes static and more viscous leading to bacterial infections in the lungs.

Cystic Fibrosis does not just affect the lungs in some cases. Occasionally, the pancreas and in the case of men, reproductive organs can be affected. This all depends on which class of mutation of the CFTR gene the patient has as

patients with Class I, II and III are prone to pancreatic insufficiency3. In normal pancreatic exocrine secretion, the digestive enzymes secreted from pancreatic gland cells, are mixed with a bicarbonate-rich fluid, secreted from duct cells and released into the small intestine to aid in the digestion offood. The function of the pancreatic gland cells remains fairly constant, but there is a noticeable difference in secretion of the bicarbonate-rich fluid from the duct cells. Thickening secretions causes the duct releasing fluids into the small intestine becomes blocked by enzymes precipitating as well as mucosal build up. With the ducts becoming more blocked, the pressure inside the pancreas increases and as the pancreas lacks structures aiding in support is therefore very prone to damage.

Symptoms

Cystic fibrosis effects different organs around the body and therefore gives rise to a vast range of symptoms. The organs most heavily affected by cystic fibrosis are the lungs and the pancreas, and in males, the reproductive organs are affected.

The most obvious indication that a patient may have cystic fibrosis would be afamilyhistory of the disease. As cystic fibrosis is a genetic disorder, the faulty recessive gene can be passed to children. Due to the gene being recessive, it is possible for parents to be a carrier for cystic fibrosis but not express any symptoms themselves. Therefore if both parents are carriers of the gene, then there is a 25% chance of the offspring having cystic fibrosis. From 2009 onwards it is required for new-born babies in the USA to be screened for genetic disorders like cystic fibrosis. If positive, it gives doctors

an opportunity to act quickly and maybe prevent other more serious problems, related to cystic fibrosis developing later in life[7]. Other common symptoms that are shown by most ages are salty tasty skin, clubbing of the fingers and toes, coughing with sputum production, mucoid Pseudomonas aeruginosa isolated from airway secretions and hypochloraemic metabolic alkalosis[8].

The symptoms shown by the patient are also different depending on their age. Figure 2 shows a table listing the symptoms by age they become prevalent.

NeonatalInfancyChildhoodAdolescence and Adulthood

Meconium ileusPersistent infiltrates on chest radiographs Chronic pansinusitis or nasal polyposisAllergic bronchopulmonary aspergillosis
Protracted jaundiceFailure to thriveSteatorrhoea Chronic pansinusitis or nasal polyposis
Abdominal or scrotal calcificationsAnasarca or hypoproteinaemiaRectal prolapseBronchiectasis
Intestinal atresiaChronic diarrhoeaDistal intestinal obstruction syndrome or intussusceptionHaemoptysis
Abdominal distentionIdiopathic recurrent or chronic pancreatitisIdiopathic recurrent pancreatitis
CholestasisLiver diseasePortal hypertension
Staphylococcus aureus pneumoniaDelayed puberty
Idiopathic intracranial hypertension (vitamin A deficiency)Azoospermia

secondary to congenital bilateral absence of the vas deferens

Haemolytic anaemia

Figure 2 – Depending on the age of the patient, different symptoms for Cystic Fibrosis will be apparent shown in the table above8

As shown in Figure 2, cystic fibrosis has a big effect on many parts of the body. However, the main problem for a patient with cystic fibrosis remains pulmonary disease and the effect of the gastrointestinal problems which arise.

Innate defence mechanisms like the physical barrier provided by the mucous, lining the respiratory tract, is inefficient at its function in a patient with cystic fibrosis. This therefore leads high levels of bacterial infection and inflammation.

The bacterial infections begin soon after birth with Staphylococcus aureus and Haemophilus in? uenzae usually being the pioneer bacteria causing primary infection in the lungs of a patient. It has been suggested that these bacteria are responsible for damaging the epithelial surface cells and therefore aiding other bacteria bind to the surface, however this is still under debate by scientists. However, Pseudomonas aeruginosa is the organism responsible for the later, fatal infections that cause the highest mortality rate in patients with cystic fibrosis. The CFTR protein not only has functions transporting ions, but it is also thought to have a role in binding molecules of Pseudomonas aeruginosa. In a normal individual, Pseudomonas aeruginosa binds to the CFTR protein, and a rapid and self-limiting in? ammatory

response9 occurs removing the infection from the respiratory tract. This explains why Pseudomonas aeruginosa is the main causative agent of pulmonary disease in cystic fibrosis sufferers.

Symptoms of cystic fibrosis caused by gastrointestinal problems are mainly caused by the inability to digest food. As mentioned above the ducts leading to the small intestine, which would carry a liquid, containing digestive enzymes is blocked. This causes the pancreas to come pressure and gets damaged. The symptoms caused by this inability to digest food are greasy stools, flatulence, abdominal bloating, and poor weight gain8. At the time of its discovery, malnutrition was the main cause of death due to the inability to produce the enzymes in the pancreas to digest food. Malnutrition can now be treated using pancreatic enzyme replacement therapy8, however other factors like the poor adsorption of fat soluble vitamins can lead to acrodermatitis, anaemia, night blindess, neuropathy, osteoporosis and bleeding disorders8.

A high percentage of Cystic fibrosis patients can develop Cystic Fibrosis relatedDiabetesMellitus (CFRD) due to the pancreatic damage that is done by the blocking of the ducts within in the pancreas. The Islet of Langerhans produces insulin and glucagon to regulate blood glucose concentrations. Insulin stimulates the formation of glycogen, removing glucose from the blood stream whereas glucagon stimulates the breakdown of glycogen. With the pancreas undergoing autolysis, it is inevitable that these cells will become damaged and unable to produce a sufficient amount of insulin. However, CFRD is different to diabetes mellitus I and II. The specific

symptoms affected by cystic fibrosis are glucose metabolism, acute and chronic infection, glucagon deficiency, liver dysfunction, decreased intestinal transit time, and increased work of breathing8.

Cystic fibrosis also affects male reproduction. In the male reproduction organs, the vas deferens is responsible for the transfer of sperm from the epididymis in anticipation of ejaculation8. Male patients with cystic fibrosis lack this muscular tube and therefore there is no sperm in their ejaculate. Women however are fertile, but careful control of nutritional intake must be taken to ensure the full term of pregnancy and subsequent birth can be achieved. I can be possible for parents to pass the gene for cystic fibrosis onto their children. As a man expressing the disease being infertile the recessive gene must come from a carrier of cystic fibrosis but not expressing any symptoms. If the female sufferers from cystic fibrosis then there is a 50% chance that the child will also have the disease. However if the female is also a carrier of the recessive gene then there is a 25% chance that the child will have cystic fibrosis.

Current Treatments

As it stands at the moment, cystic fibrosis cannot be cured. Cystic fibrosis is a genetic disease, and therefore there is an error in the DNA of cells of an individual apart from their gametes. This means that the only available option to sufferers is to find drugs to treat the various symptoms. However in recent years there have been successful attempts to find drugs to resolve the original defects.

Patients with cystic fibrosis often suffer from severe pulmonary infections, as they are less efficient at swallowing mucous containing pathogens. The airway surface liquid and cilia, as discussed above are responsible for the movement of mucous up the respiratory tract in a normal individual. Cystic fibrosis sufferers lack the required volume of airway surface liquid. One such treatment, looking to solve the problem caused by the faulty gene is hypertonic saline. Hypertonic saline is the current drug used to bring about an increase in the volume of airway surface liquid in the lungs of the patients. It has been shown by researchers that in vitro, hypertonic saline is effective with rehydrating and providing more airway surface liquid8. If from an early age there is aid with mucosal clearance from the respiratory tract, it would reduce the chances of the patient developing severe bacterial infections from pathogens such as pseudomonas aeruginosa.

Antibiotics are also important to control pulmonary bacterial infections that occur from poor mucosal clearance. Macrolide antibiotics are cheap antibiotics used to treat cystic fibrosis sufferers. They work by inhibiting the bacteria protein biosynthesis; however the precise mechanism they use is currently not fully understood. Macrolides have a dual function in the cystic fibrosis treatment. They affect cytokine production of many cell types and are therefore effective as anti-inflammatory agents8. One study showed that taking azithromycin three times a week reduced the virulence factor production, decreased biofilm production, bactericidal effects on pseudomonas aeruginosa growing in stationary phase8.

Patients with gastrointestinal symptoms brought about by cystic fibrosis require other forms of treatment, as they unable to produce enough enzymes to digest their food. Enzymes are usually secreted from the pancreas into the small intestine, allowing the individual to digest their food. However a patient with pancreatic insufficiency is unable to secrete the enzymes into the small intestine due to the intrapancreatic ducts being blocked. This needs to be treated as patients are at risk of severe malnutrition if food cannot be fully digested. Pancreatic Enzyme Replacement Theory (PERT) is used to treat this problem. The enzymes used in PERT are taken with every meal to aid in the absorption of food in the small intestine. This does not solve the underlying problem caused by cystic fibrosis, and can only treat the symptoms. This is because the enzymes do not last for a great deal of time in the body; the reason why enzymes must be taken with every meal.

Chest physiotherapy can aid in the treatment of a sufferer as it can help in mucosal clearance from the pulmonary tract[11]. Some methods focus on the way the patient breathes which include active cycle of breathing techniques, and autogenic drainage11. However some techniques focus on actual mucosal clearance like positive expiratory pressure (PEP) oscillating positive expiratory pressure11.

The final and most severe treatment used to use the chronic pulmonary disease is lung transplantation. This procedure comes with high risk with only 50% children surviving 5 years after the transplant and 50% of adults surviving 6 years after the transplant8.

Future Treatments

As of yet there is no cure for cystic fibrosis, however there are promising new drugs on the horizon which could one day all but cure the genetic disease.

A drug that is combatting the “ basic defect” of cystic fibrosis is VX-770 made by Vertex pharmaceuticals. This drug is currently undergoing trials in the United States of America and is showing promise for improving lung function in those affected by cystic fibrosis. The drug itself targets the chlorine channels in the apical membrane, opening them to allow chlorine to leave the epithelial cells. Results from the recent Phase 3 clinical trials showed that there was a 10% increase in lung function in people aged 12 and above, and a 12. 5% increase in lung function for those from ages 6 to 11. The drug also decreased the concentration of chlorine in sweat and allowed the patients taking the drug to gain on average 7 pounds12. Pancreatic insufficiency usually makes it hard for the cystic fibrosis patient to gain weight, meaning the drug has an effect on gastrointestinal symptoms as well as respiratory symptoms.

The idea of gene therapy is a concept that has been around for a while. The Cystic fibrosis gene therapy consortium was set up in 2001 to focus on developing new ways to combat cystic fibrosis and the symptoms. In February 2009, the consortium made a step closer to find a “ gene therapy cure” for cystic fibrosis. They managed to insert successfully, a working CFTR gene into a viral vector, which was then transported into the lungs of a cystic fibrosis patient. Whereas the idea itself is good, there are some drawbacks. The viral vector itself comes under attack from the immune system as well

as viral vectors being poor at inserting DNA into epithelial cells8. Therefore the The Cystic fibrosis gene therapy consortium has been looking at using lipid vectors currently with little success. They have reported that currently gene expression in the cells that do take up the gene is currently temporary and they are looking into methods to provide sustained gene expression in the epithelial cells.

Not all mutations cause the CFTR protein not to be synthesised. Some mutations cause the CFTR protein to be marked for degradation as the chaperones, aiding with folding the protein, do not dissociate from the protein8. There have been tests in labs using chemicals such as phenylbutyrate8, however any further developments in this field of research.

Conclusion

It is remarkable how such a small difference in the DNA of an individual can have so much effect on the patients’health. However the future looks bright for those patients suffering with cystic fibrosis. There is a huge amount of research taking place in order to find new treatments and potential cures for the disease. Recently, research has shifted from looking for ways to treat the symptoms, to methods of treating the underlying problems behind the disease. For example a drug called VX-770 made by Vertex Pharmaceuticals, focuses on the inefficient chlorine channels in the epithelial cells. If cystic fibrosis remains a continually financially backed area of research, there is no reason why significant progress cannot be made sooner rather than later.