APPLICATION OF NANOTECHNOLOGY IN USE FOR TREATMENTS AND DIAGNOSIS OF BRAIN, HEART, FERTILITY AND DIABETES DISEASE.

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Abstract

The term 'nanotechnology' encompasses the use of materials created and manipulated at nanoscale, which are then utilized for human benefit. Currently there is a lot of research into the uses of nanomaterials such as nanofibres, nanotubes and nanomachines, and especially as to how such substances could be exploited for their medical uses. This paper explores some recent research into treatments for brain and heart disease as well as fertility and diabetes. Additionally the paper indicates future applications.

Introduction

The Brain

The brain is the body's control centre, controlling thoughts, memory, speech, movement and organs. When healthy, the brain works quickly and automatically. However, when problems occur, the results can be devastating both for the individual and their friends and family. Research into diagnosis and cure of brain disease has taken a variety of forms, detailed below.

Restoring lost abilities

Researchers have investigated how injecting a fluid containing amino acid chains into a damaged area could 'bridge the gap' created by a stroke or fall. Initially they cut into the area that conveys signals for sight in rats, causing blindness, before injecting fluid containing the amino acid chains which consequently bonded, assembling into nano-scale fibres in this area of the brain. The interwoven fibres inhibited scar tissue forming while encouraging cell growth.

Carbon Nanotubes

European researchers have looked into repairing damaged brain tissue using carbon nanotubes. The findings highlight that carbon nanotubes are excellent electrical conductors and can form intimate contacts with cell membranes, so allowing a functioning route to neuron structures improving neuronal performance. Figure [1], depicts a web of carbon nanotubes.

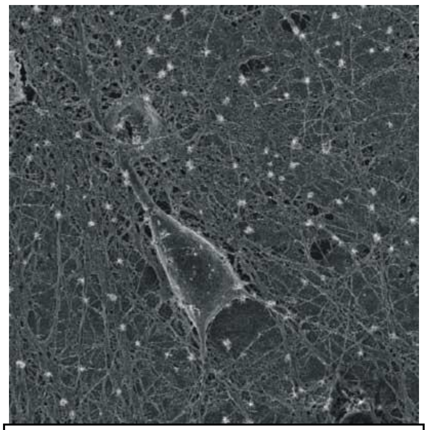


Figure [1] TSEM micrograph of a cultured rat hippocampal neuron grown on a layer of purified carbon nanotubes

Destroying Bacterial and Fungal Cells

Some brain diseases, such as meningitis which is fatal and can cause irreversible brain damage in patients, are caused by an invading pathogen. Researchers at the Institute of Bioengineering and Nanotechnology have experimented into bioengineering nanoparticles that seek out and destroy bacterial and fungal cells that cause such infections.

Coating for brain implants

Biomedical and materials engineers at the University of Michigan have researched increasing the life span of brain implants, because current devices start to lose function after only a few months.

The new coating that the researchers developed are created from three components, which together allow the electrodes to work more smoothly with the brain. The nanoscale polymer (named PEDOT) enables the electrode to operate with a decreased electrical resistance, meaning they can communicate more effectively with the individual neurons of the brain, while the alginate hydrogel gives the devices properties similar to actual brain tissue to reduce the damage caused by implementing such devices. Finally, the nanofibres stop the immune system destroying the device.

Diabetes

Diabetes is a common life-long condition, which is a disorder of metabolism. There are 2.8 million people living in the UK currently diagnosed with diabetes, and a further estimated 850,000 who are yet to be diagnosed. Having diabetes doubles your risk of having heart disease and diabetic retinopathy is the leading cause of blindness in American adults. This makes diabetes an important condition to cure and diagnose, not only because of the improved quality of life given to sufferers but the enormous medical and economic strain that it puts on society.

Typically, sufferers of diabetes have to prick their finger up to three times a day to monitor their blood glucose levels, in a process, which is both painful and tedious. However, a new world of opportunity has been opened, both in the areas of diagnosis and cures, in the form of nanotechnology. Although applications of nanotechnology in diabetes are in their infancy, there are many ideas and experiments for how new, effective treatments could come about.

Artificial Pancreas

The original idea of an artificial pancreas came 1974. It is a relatively simple idea, consisting of a sensor electrode, which constantly monitors blood glucose levels, feeding data into a computer located in the artificial pancreas to analyse and use the information to control an infusion pump; which feeds insulin into the bloodstream. This reason was abandoned in the 1970's because a large, powerful computer was required for such a vast amount of information. New advances in nanotechnology, means a system is no larger than an average sized human pancreas is achievable.

Medtronic MiniMed, an American company, is working on a device that incorporates an implantable long-term glucose sensor with an implantable insulin pump. The main problem is in designing an algorithm, which can take the blood glucose levels and transform it into appropriate insulin doses.

Nanomachine inserting new genes

Researchers at the Sansum Medical Research Institute, Santa Barbara are researching using nanomachines to insert new genes into naturally occurring cells which would be altered to respond to changes in blood glucose levels whilst producing insulin if necessary, mimicking the actions of normally functioning pancreatic.

Dissolvable Matrix

This idea suggests that a matrix (such as that of the buckminsterfullerene) could contain a dose of insulin, which would dissolve in contact with glucose molecules, slowly releasing the insulin into the blood.

Diagnosis of diabetes

Professor Pratsinis and his team have experimented creating a sensor coated with a semi-conductor made of nanoparticles to give extreme sensitivity. Suffers of type 1 diabetes have unusually high levels of acetone in their breath (1800ppb or more compared to the norm of 900ppb). The sensor they manufactured can detect this increase in acetone.

Coronary Heart Disease

Coronary Heart Disease is the UK's biggest killer according to the NHS with around one in five men, and one in seven women dying from the disease.

Whilst treatment for cardiovascular disease vast, surgery is often the most effective form of treatment, however through use of nanotechnology, invasive surgery can be avoided, ultimately benefitting the patient with less discomfort and inconvenience caused.

Research has been performed into using nanotechnology to treat and prevent heart disease in several different areas including the treating of defective heart valves, and detecting and treating arterial plaque.

Treating defective heart valves

Researchers at the University of South Carolina and Clemson have experimented combining gold nanoparticles with collagen protein. If the heart valves have the wrong level of collagen their ability to effectively function is impaired: too little collagen and the valve becomes floppy, but too much and it becomes stiff, whilst in both circumstances the heart has to work harder and is put under more strain.

Detecting and treating arterial plaque

There are several initiatives regarding the removal of arterial plaque, including research at The State University of New Jersey, UC Santa Barbara, and Harvard medical school.

Fertility

Reduced fertility is a sensitive and common problem globally, with a vast spectrum causes, ranging from Klinefelter's syndrome to a low sperm count.

Nanotechnology, although appearing as an innovative solution to problems such as diabetes, may not be the solution to infertility, but in fact a cause. Research performed into nanotechnology's impact upon fertility includes the following.

<u>Sperm Cell Growth</u>

Silver nanoparticles used in consumer products were identified in 2010 as being able to interrupt cell signalling within male reproductive cells, inhibiting their growth.

<u>Hormone monitoring</u>

Scientists at the California Nanosystems Institute have initiated a start-up company to conduct early-stage research into developing a hormone sensor for biomedical applications in infertility and menopause related areas.

The investigating technology considerably increases hormonal detection sensitivity beyond that of traditional sensors, and involves the use of nanoelectronic technologies.

<u>Fertility monitoring</u>

Researchers at the University of Twente's MESA and the Institute for Nanotechnology have developed a 'fertility chip' which can accurately count spermatozoa in sperm.
This is an important step towards the development of compact devices for reliable 'pre-scanning' of male fertility.

Discussion

Brain

Research stated earlier proves that amino acid chains, when introduced to the environment of the brain, assemble into nano-scale fibres, which encourage brain tissue growth. This knowledge could be applied if, once brain surgery has occurred such as the removal of a tumour, the surgeons inject the described fluid containing amino acid chains before stitching up the patient to increase the chances of the patient recovering, as the nano-scale fibres would encourage healthy brain tissue to grow. Additionally, future research should be done to look into whether nanofibres encourage tissue growth elsewhere in the body, and if so, this knowledge could be applied in the lab to create artificial organs. A skeletal blueprint of the organ required could be created (research into this procedure would need to be undertaken) and then a layer of nano-scale fibres placed on top. Stem cells could then be introduced and encouraged to grow on the 'skeletal' organ by the nanofibres thus creating a fully functional organ if all the necessary cells were grown. This would be extremely beneficial as the NHS would no longer have to rely on organs donated by the deceased for surgery, instead growing the needed organ in the months leading up to the operation. This would additionally remove the ethical problems of organ transplants (some religions, such as Jehovah's Witness, are wary of organ donation) as the organs were never in another living organism – they are completely artificial.

Carbon nanotubes are a useful substance that have interested the media. Further work regarding how carbon nanotubes could be used to improve brain function include replacing metal parts in clinical applications to give more effective deep brain stimulation for the treatment of Parkinsons disease alongside other applications. Markham, head of the Laboratory of Neural Microcircuitry, stated, 'The new carbon nanotube-based interface technology discovered together with state of the art simulations of brain-machine interfaces is the key to developing all types of neuroprosthetics – sight, sound, smell, motion, vetoing epileptic attacks, spinal bypasses, as well as repairing and even enhancing cognitive functions.' As carbon nanotubes are excellent electrical conductors it follows they are excellent heat conductors also. A potential cure for cancer could come about if you placed millions of carbon nanotubes within a cancerous tumour, and somehow heated them externally (possibly by targeting high frequency waves, such as x-rays at the cancerous area), the carbon nanotubes may heat to a point where they kill the cancer cells.

Furthermore, the hollow feature of carbon nanotubes evokes the idea of encapsulation – drugs or other substances being carried inside carbon nanotubes to infected areas. If you combine the knowledge of the dissolvable matrix which was created when researchers were looking into cures for diabetes, with the fact that carbon nanotubes are hollow, you could possibly use carbon nanotubes as a pill that dissolves when it gets to the infected area, or when it meets the right particle.

The technology behind creating nanoparticles that can pass through membranes is extremely useful in all medicine because the origin of all disease starts at cell level and is normally some function in the cell not functioning correctly. Therefore it is very important that we can create drugs and nanomachines that are permeable to cell membranes in order for the cure to reach and cure the start of the problem. This technology could lead to nanomachines repairing sections of DNA that have become damaged (which previously have been unreachable as DNA in eukaryotic cells – the type found in human bodies – are enclosed in a double membrane), or could even lead to new oral drugs encased in nanoparticles passing through the intestine lining to the blood stream where the surrounding nanoparticles then disintegrates, releasing the drugs to have effect on their target organ. This is important in curing currently incurable diseases, because at the present time the main treatment for such disease is to try and reduce systems rather than to cure the actual problem. Additionally, nano-machines could be created that are capable of turning genes on and off. This would be extremely useful as a cure for a number of genetic diseases as the dysfunctional gene could merely be switched off before it affects the organism as a whole.

Finally, the nanofibres mentioned in the introduction may be very useful if applied to organ transplants (see notes on the new coating that the researchers developed, which have been proven to not be attacked by the body's' immune system due to the nanofibres coating). One of the biggest problems of organ transplants at present time is the fact that the patient must take powerful immune-suppressants to ensure the body's immune system does not destroy the new organ as it has been recognised as 'foreign'. If all organs that are transplanted had either a layer of the nanofibres, or even had entwined into their structure some of the nanofibres, then this would significantly reduce the need for immune-suppressants because the nanofibres would ensure the immune system didn't attack the new organ. This would not only be more cost effective, but extremely beneficial to the patient as the immune-suppressants can often have side effects such as the body is very vulnerable to opportunistic infections, even those usually considered harmless. Also, prolonged use of immuno-suppressants increases the risk of cancer.

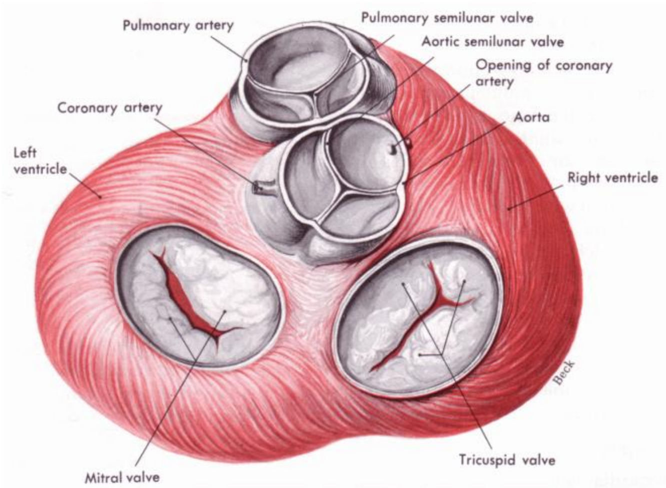
Diabetes

Future developments of nanomachines, as well as use in an artificial pancreas could be to create a nanosized microscope, which would be used to look at DNA. This could diagnose a disease at molecular level, rather than relying on diagnosis from symptoms, which is an unreliable process. The time saved could make the difference in saving lives. Furthermore, nanocameras could be ingested. These could be created to take themselves to a specific area in the body, and relay real-time images of the damaged area. This would be extremely helpful in keyhole surgery, allowing great precision, and creating minimal damage to healthy cells.

Finally, the breath analyser created using nanoparticles is a very interesting idea for future diagnosis of disease. Professor Sotiris Pratsinis hopes that other chronic illnesses could be detected using such a device, and we believe that if this occurred, it would revolutionize diagnosis of disease. Not only would GPs find their job far easier, but also in hospitals, rather than trying to find out whether a patient has any ailments in an emergency, you merely would need to breath analyse them for any major illnesses. This would not only save huge amounts of time, but also lives. Finally, if you managed to bring the price of such a device down, every household could own one. This would allow many illnesses to be flagged at an early stage, making it far easier for doctors to cure. To make this achievable, future research should be undertaken to see whether there are any 'indication chemicals', such as the acetone for diabetes, which could be detected in peoples' breath for other illnesses.

Heart disease

Figure [2]: cross section of healthy heart



The valves of the heart viewed from above. The atria are removed to show the mitral and tricuspid valves.

Researchers have found that by modifying the nano-sized gold particles with polymers they can create a charge that affects the assembly of collagen, eliminating the need for corrective surgery. When exposed to these nanomaterials, collagen production by fibroblasts is altered and so is the phenotype of the cells. Further proposed research is to measure the collagen-fibroblast-nanoparticle's mechanical properties, with the notion of potentially permanently correcting the valves' collagen composition, this being enormously beneficial to a patient who would otherwise have to endure surgery and a recovery period. Further research to consecrate the discovery could be to ensure that the polymers used are the most effective; as if the treatment was adopted the risk of deterioration should be as minimal as possible. This would prevent such deterioration of the heart that a heart transplant would be needed, and thus (similarly to that of nanotechnology methods in encouraging brain tissue) hugely benefit the patient. This research also has the potential to reduce scarring.

Additionally, researchers at The State University of New Jersey have experimented with nanoengineered molecules called 'nanolipoblockers' which combat clogged arteries, by attacking the means in which LDLs trigger inflammation and plaque build up at specific blood vessel types The nanolipoblockers bind to the receptor sites on macrophages to reduce the accumulation of oxidized LDL. Further in depth research involves specifically altering the nanolipoblocker structure by changing the groups on the chain ends and closely analysing which forms of the particles bind to the different macrophage receptors. Whilst systemically active drugs have made significant headway in preventing cardiovascular disease, they have not succeeded in universally addressing the recurrence of inflammation and blockage of stent surgery sites whilst nanolipoblockers have the potential to so.

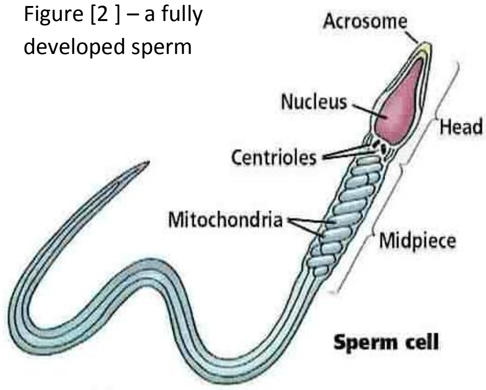
Scientists and engineers at UC Santa Barbara have collaborated with other researchers to develop a nanoparticle that specifically detects atherosclerotic plaques. The nanoparticles in this case are lipid-based collections of molecules that form a sphere called a micelle, which has a peptide on its surface that binds to the surface of the plaque. The micelles attack the areas where plaques are prone to rupture in mice. This has the potential to be translated for human use and would work effectively if treatments which widen the lumen of clogged arteries were ineffective or preference.

Researchers at Harvard medical school have engineered nanoparticles called 'nanoburrs' designed to attach to artery walls and slowly release drugs, which treat and prevent plaque build-up there (specifically the basement membrane of the artery which is only exposed when the artery is damaged). Each nanoburr is coated with protein fragments that allow it to stick to the membrane, whilst its core particle contains a drug, which is bound to a polymer-like molecule and is slowly released, combating the narrowing of blood vessels. This technology could potentially have broad applications across other important diseases, such as cancer and inflammatory diseases, and we suggest that further research could be to intravenously inject the 'nanoburrs' into mammals with a cardiovascular system more relatable to humans. In regards to all of these research projects there are ethical issues regarding animal rights, however, in our opinion, the high proportions of deaths from cardiovascular disease annually, deem this research as both necessary and promising for future treatments.

Fertility

The study that looked into sperm cell growth involved a cell line of mouse sperm cells, on which the effects of varying sizes, concentrations and coatings of silver nanoparticles upon cell growth were tested. Results revealed that exposure to the particles with the smaller diameters led to more cell deaths, and that those coated in sugar increased the production of reactive oxygen species (ROS) – one of the signals for induced cell death.

Figure [2] – a fully developed sperm



As a result, there is heightened awareness about the potential impacts of nanoparticle use in consumer products upon male fertility, but additionally, research has been evoked into other areas of fertility, such as after conception where there is evidence that exposure during foetal development can lead to birth defects related to the male reproductive system as silver nanoparticles are able pass through the placenta. Potential future studies based upon this research should be performed upon a mammal with a reproductive system more similar to humans'.

A U.S-Chinese research team investigated the impact of carbon nanotubes upon male fertility by periodically intravenously injecting a nanotube suspension through the tail vein into healthy adult male mice so as to mimic potential biomedical applications in terms of method and dose. The results however have contrary implications to those of the above study. Although within 24 hours of the first injection, nanotubes were accumulating in the testis causing oxidative stress and tissue damage, this was reversed after two months and there were no observed effects upon male fertility, delivery or foetus viability under their experimental conditions. Furthermore, sex hormones and sperm were unaffected by the nanotubes throughout the 90-day period and treated mice produced healthy offspring. Similarly however, the testes of the mice treated with five does of carboxylated nanotubes were characterized by partially damaged seminferous tubules, a considerable reduction in the thickness of the germinative layer, and a reduction in the number of spermatogonia, hence further research should be conducted focusing upon the affect of carbon nanotubules in these areas.

Scientists at the California nanosystems Institute are investigating technology which increases hormonal detection sensitivity beyond that of traditional sensors, and involves the use of nanoelectronic technologies with the aim of developing a consumer-based, simple-to-use sensor for detecting oestrogen and progesterone hormone levels. This would help women in qualifying unwanted menopause symptoms and potentially informing couples seeking infertility treatments when conception is more likely to occur themselves, thus providing a cheaper and faster alternative to current infertility treatments. The sensor measures hormone concentrations using specially made hormone tabs (similar to glucose tabs used by diabetics) made by low-cost and precise ink-jet printing of carbon nanotubes. This system will provide on-demand hormonal levels so patients can better control drug intake related to hormone therapy, and therefore a more effective treatment course.

The proposed 'fertility chip' has huge potential to being adopted as a treatment for male fertility in the short term, and female in the long. Additionally, as the chip is of nano-proportions, the patient will have minimal discomfort, yet the information gained for prospective parents will be invaluable. Ethically, these treatments evoke conflicts over animal rights because they have been tested on without consent and as effective fertility treatments are already available the tested can be deemed unnecessary.

Conclusion

Concerning the brain, we conclude that the research looking into inserting new genes into naturally occurring cells using nanomachines would be the most beneficial in treating not only brain disease but a whole array of body disease. We believe this because most disease starts at DNA level and so to modify cells to carry out their function perfectly, you could cure the body of almost all ailments.

Through looking at research into cure for diabetes we conclude that a sensitive sensor that can measure the concentrations of different chemicals in the breaths of humans will be most useful in the future. We believe that a whole host of diseases could be diagnosed in this way, and it could become the norm for every family to have such a device, and use it regularly to ensure that they are healthy.

In regards to targeting Coronary Heart Disease we conclude that whilst research remains relatively premature future treatments based upon the application of nanotechnology or derived products would significantly reduce the need for surgery. Research into reducing arterial plaque has resulted in several potential methods, which is beneficial as not all are likely to be able to fully translate into practical medical use.

Regarding the effects of nanotechnology in infertility, the potential consumer hormone monitor stands out to be the most significant breakthrough, as the research into the implications of nanotechnology on sperm developing does not fully correlate. The monitor would benefit prospective parents globally if made purchasable, and potentially could help third world countries control their birth rates in being used as a contraceptive aid. Although education into using and understanding the monitor would need to be given, it could significantly influence the number of unwanted children born.

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