

Peptide nanorods and their
possible usage in regeneration of
heart tissue post myocardial
infarction.

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Research paper based on
pathology lectures at Medlink
2010

ABSTRACT

Referencing the recently published works on optical nerve regeneration in hamsters using peptide nanorods this paper explores the medical possibilities that this could lead to in future years. The central aim is to provide a possibility of non-invasive and hopefully fully corrective post myocardial infarction treatment using the science discovered in these experiments and in surrounding fields closely related to nanotechnology such as microscopy. The paper explores current scientific knowledge and questions the future path it may follow concerning ethics and evolution.

INTRODUCTION

The development and importance of nanotechnology;

Nanotechnology, the study of structures smaller than 100nm has advanced vastly in recent years. This is of course mostly due to technological advancements; the development of the scanning tunnelling microscope (Binnig and Rohrer 1981) has allowed structures smaller than cells to be seen in great detail and has hence allowed scientific understanding to advance much further than before. This plays a vitally important role in the development of medicine as the building blocks of human life are on such a small scale, take proteins, enzymes and DNA as an example, the hydrogen bonds that are vital to the maintenance of the highly specific shapes can now be seen, despite measuring only 0.25nm in diameter! Much more is known about the body now that we can see much finer details thus allowing for new treatments to be developed that deal with the root, and often extremely small cause of diseases and ailments.

Manipulation on such a small scale;

Not only can we now observe such small structures, but we can also manipulate them. This has been demonstrated by scientists such as Ho and Lee, Cornell University in 1999 when using a scanning tunnelling microscope they moved a single carbon monoxide molecule, CO, onto a single iron atom, Fe and bound them together using a voltage. This showed that positional molecular assembly is indeed achievable, disproving the earlier thoughts of Smalley who believed that mechanosynthesis such as this was impossible as it was too difficult to manipulate individual atoms.

The microscope works by 'tunnelling' electrons between a very small gap (around 2nm) between the tip of the microscope and the sample. By doing this a complex image of the surface of a sample can be built. The electrons are extremely sensitive to voltage, so when the tip is moved across a sample surface any variations in voltage are measured, allowing a picture to be built, in a not entirely dissimilar way to how modern ultrasound scanners work.

Current medical use of nanotechnology;

With respect to medicine, one of the most important advances in nanotechnology to date has been the creation of the Fullerene family of carbon spheres, namely the sphere with a molecular formula of C₆₀ named a Buckminsterfullerene, or 'Buckyball'. The relatively simple idea of a hollow ball has begun to and will continue to revolutionise drug delivery. As it stands, much more of a drug than necessary has to be given if it is taken orally due to the effects of digestive enzymes and pH of the stomach which can denature proteins within a drug and can drastically decrease the usefulness of the drug. (Bernkop-Schnürch and Krajicek 1998) This is where these carbon spheres are useful; a drug can be placed

inside a 'Buckyball' (Smalley 1996) and will be protected as it passes through the digestive system, to be released when it reaches its specific destination. In the future, this could prove to be especially useful in the delivery of insulin to diabetic patients, especially children. It could mean a much higher success rate in the management of diabetes as children will of course be much more inclined to take a tablet than to inject themselves with a drug up to three times a day.

Possible pit-falls of nanotechnology;

Yet, with new power and knowledge comes a great deal of ethical responsibility. The environmental effects of nanoproducts have not yet been proven and there are fears, voiced by the Center for Responsible Nanotechnology that this new knowledge and understanding could indeed lead to huge threats such as untraceable weapons of mass destruction. Seemingly minor issues that could lead to large environmental consequences are beginning to be seen, one particular example would be that of silver nanoparticles used to reduce foot odour in socks are being released when washed and are in fact killing useful bacteria needed for the breakdown of organic products, especially in waste treatment centres due to the antiseptic nature of silver. There are many further examples of the negative effects of nanoproducts, which will be explored in the discussion of ethical responsibility.

The problem to be addressed;

There is a worryingly high death rate due to myocardial infarction in today's world. What is also concerning is that after one heart attack, a patient may go on to suffer many more before one final, fatal attack results in their death. If the number of attacks can be limited to one then the death rate due to heart attacks could be greatly reduced. Within the paper, possible ways of restoring full heart health and hence preventing patients from suffering multiple heart attacks will be explored.

DISCUSSION

Current understanding of the workings of tissue regeneration;

One advance that is particularly exciting within nanotechnology is that of regeneration of the optical nerve in hamsters. (Rutledge G. Ellis-Behnke 2006) Outstanding results were seen in the hamsters; after the optical nerve had been surgically severed, the site was injected with synthetically made peptides of 5nm length. These fibres spontaneously arranged themselves and hence built a scaffold for brain tissue and later nerve tissue to grow around. What was truly astounding and equally unexpected is that tissue began to re-grow within just twenty-four hours of peptide introduction and further that it was not scar tissue that grew but normal brain tissue. This effect would perhaps have been expected in young hamsters whose networks of neurones within the brain were still developing, but this would not have been expected in older hamsters whose brain tissues had stopped developing. With the use of these peptide nanorods, the adult nerve also recovered and functional vision was restored to all animals tested. These peptides were also shown to be broken down into harmless substances and excreted via the urine three to four weeks post introduction into the body. The scientists working on this research project hoped that this discovery could eventually help to limit damage during

neurosurgery or even help to reconnect parts of the brain post trauma, especially post stroke.

If this can be achieved with nerve tissue, a tissue that usually takes years to regenerate and re-wire as shown by the long and slow recovery of stroke victims with some patients never recovering and others rarely making a full recovery from a serious stroke then surely this new technology can be adapted and applied to other parts of the human body.

The need for a new treatment;

One of the biggest killers of today's society is heart disease; as a society we are significantly less healthy than we should be with obesity, alcohol, smoking and an extremely stressful lifestyle contributing to an overall negative health effect. It is therefore, no wonder that 25% of all deaths worldwide each year are due to heart disease; this is an incredible 12 million people every year. 25000 people die every single day of a heart attack in the United States. With figures such as these, surely there needs to be a much more pragmatic solution in place to deal with the very imminent threat that faces such a large proportion of the population.

A myocardial infarction;

With relation to the peptide nanorods and their usage in treating heart disease I would like to cite one specific problem within the umbrella of heart disease.

In the event of a myocardial infarction, part of the coronary blood supply is cut off resulting in death of cells in the area affected due to lack of oxygen supply for a period of time. This can of course be caused by an atheroma, embolism, or thrombus. It would of course be much more efficient to treat the problem early on and remove such threats to the health of the heart using nanotechnology in a way which Park Jong-oh (Chonnam National University 2010) has done. If the usage of such nanobots became common and early signs of heart disease were recognised and removed there would only be a small need for critical cardiac care. There does however still have to be a treatment plan in place for those that have suffered a myocardial infarction. Post infarction, the ability of the heart muscle to contract efficiently and to hence pump blood to the lungs and around the body is reduced. The heart is the most vital muscle in the body so regeneration of this muscle could save thousands if not millions of lives per year.

Stem cell use and its ethical concerns;

It is already suggested that stem cells could be used to re-build the muscle tissue. However, this is not without its own misgivings. Stem cells used are currently harvested by forming an embryo and using the pluripotent cells that are produced in early cell divisions before specialisation. These cells when put into the correct environment can develop into cardiomyocytes- heart cells. Treatment using stem cells and stem cell research results in the destruction of millions of embryos per year raising the question especially amongst ethicists and religious believers of is it our right to be able to create and destroy life as and when we see fit. It is here that the use of nanotechnology over stem cell use can be seen as highly beneficial.

Adapting peptides to suit a different environment;

If we are to apply the work of Ellis-Behnke with adaptation of the peptides to suit the different environment of inside the pericardial sac and to be more suited to scaffolding muscle re-growth over brain tissue then there is a huge potential for development in post

infarction treatment. Ellis-Behnke has shown that nerve tissues can regenerate around such a scaffold which proves to be advantageous to its use in heart muscle, as not only could the muscle be regenerated but also the nerve fibres that carry impulses causing contractions within the heart- there is possibility to grow people a new natural pacemaker rather than surgically insert a box to generate the electrical signals. As well as such exciting possibilities Ellis-Behnke's work also showed that the nerve regenerated without scar tissue, possibly due to a property of the peptides, but it is not fully understood why such a phenomena occurred. If the same effect can be demonstrated in cardiac muscle then a fully functioning heart can be restored, and a normal lifestyle can be resumed.

Introduction of peptides to the body;

The one major issue to overcome in this situation is that of getting the peptides into the heart muscle. The proposed entry would be via injection, the procedure being performed in much the same way as a pericardiocentesis procedure. (see Figure1.) This is a relatively non-invasive procedure so patients could return home almost immediately (except in critical cases) hence reducing numbers on wards. It also removes the need for post-operative after care that is associated with some conventional treatments of myocardial infarction such as transplant or insertion of an artificial pacemaker.

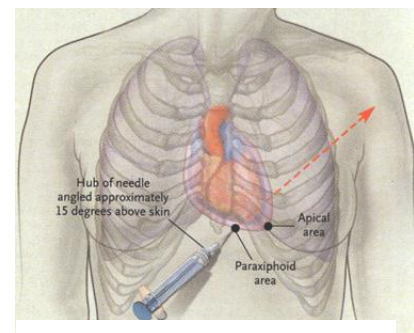


Figure1: theoretical pericardiocentesis procedure

Ethical issues raised;

If we are to assess this ethically, there are a number of dilemmas that are raised. After laboratory and animal testing, which brings its own ethical tests, this method would eventually have to be tested on a real patient that has suffered from a myocardial infarction. Depending on the severity of the attack, this can be a very unstable place to be health wise. It is for this reason that it is only appropriate to trial the treatment on patients who suffered only a mild heart attack. With an estimated delay of around 24 hours before any noticeable difference can be seen, the treatment would not be a sensible consideration for a patient in a critical state. At that point, 24 hours is too long to wait and would most likely result in the death of the patient as to scientifically test the procedure correctly all other treatments would have to be suspended. This is not ethical as it would gravely endanger the life of a critical patient. It is hence much more justified to pilot this new method on otherwise healthy patients that have had a good post infarction recovery. This would ascertain how good the peptide nanorods are at building a scaffold for new muscle to form around and also how effective they are at stimulating nerve growth; the ultimate aim is not only to build new muscle, but to build new muscle that will contract at the appropriate time within the cardiac cycle restoring full working function to a patient that would otherwise have not experienced a full recovery.

One final ethical point to consider is the environmental effect and safety of nanoproducts. There is plentiful evidence to suggest that some of the nanoproducts that are being developed are having a negative effect on the environment, humans and animals. In addition to the environmental problems mentioned in the introduction, there are many other reported cases of damage caused by nanoproducts. A study conducted at The

University of Rochester found that nanoparticles inhaled by rats in a laboratory settled in the brain and lungs and increased the production of biomarkers for inflammation and stress response. Within the human brain this could have especially severe consequences such as brain damage. A Chinese study found that some nanoparticles induced skin ageing in mice, which would not only be undesirable concerning the health of the skin but also in the current social climate this would be hugely cosmetically undesirable. One particularly worrying result was obtained from a study at the UCLA School of Public Health. The study found that mice that had been ingesting nano-titanium dioxide suffered damage to chromosomes and hence to the DNA structure. The alteration of chromosomes within the DNA is a fault that is associated with cancer. It is here that we see some of the serious possible consequences of the use of nanotechnology. It is however, only like any other new medical development; it brings its own problems but these problems are not without solutions and so long as the use of nanoproducts is monitored and is responsible and adjusted as necessary then there should be no other risk to the public than with any other new medical advancement.

What impact will this have on the population?

From an evolutionary point of view, there is one major issue to address. With medical care developing at the fast pace that it is, the population is becoming older and older as a whole; many people that would have died are now surviving and living a full life, for instance children born with cystic fibrosis even thirty years ago would have died as babies or small children and are now instead living into their forties and are having children, hence passing on the gene, all be it recessive, onto the next generation. If we continue to save more and more people then surely as a race, human kind will regress and become a weak race dependant on the medical care that technology can provide. However, in this instance this argument can be for the most part discounted. The primary reason being that most cases of heart disease are due to lifestyle factors, not genetics, yes genetics can make a patient more susceptible to contracting heart disease but it is not usually the direct cause. The secondary reason is that by the time most people will suffer from heart disease, they are in the later stage of their life and will most likely have had children. Therefore, the treatment of heart disease in a much more efficient way is less of an evolutionary problem and more of a problem concerning overcrowding due to ageing populations.

Further applications of the technology;

Of course if this were to be shown to work, even on muscle fibres in a laboratory then the potential here is enormous. Such advancements in approaches to the treatment of death or atrophy of a muscle could open up a world of other possible solutions to conditions as debilitating as muscular dystrophy and could prove to be very useful in trauma cases. If we are to take for instance, an example of a patient with only a single kidney and suppose that the kidney became damaged in some sort of accident, such as a car crash and was henceforth not able to function properly. For some this could mean long term dialysis while a suitable transplant donor is found. Suppose now that instead of the patient having to be put on the transplant list they were instead injected at the site of trauma with a serum containing the peptides necessary to scaffold new tissue growth within hours of admittance to hospital. This would mean that the patient would have to be on dialysis for

a much shortened period of time, if at all depending on the severity of the trauma experienced.

CONCLUSION

If this technology were to work there would not only be huge medical benefits but also great economic benefits with vastly reduced aftercare. This vast saving could leave money that the NHS can focus elsewhere, improving quality of care elsewhere and boosting other vital resources. As with any new treatment there would of course be an extensive testing period before the drug could be proven to have a positive effect and could finally be licensed for use.

Problems to overcome;

One problem that could be difficult to overcome is that of the stimulation of two different types of tissue using one medium. Ellis-Behnke showed that the peptides provided scaffolding for glial cell growth and that neurones also re-grew. It is not known whether or not the peptides played a part in stimulating the growth of the neurones so we can only speculate as to the effect that will be had upon heart tissue. Clearly it would be of great advantage to be able to develop a peptide that will provide scaffolding for muscle growth and simultaneously stimulate the growth of purkinjie fibres that allow electrical impulses to spread across the heart muscle hence allowing contraction. If this were possible it would reduce the time needed for restoration of full heart function as there would not be such a wait as would be generally associated with natural stimulation and re-growth of nerve fibres.

There is also always the possibility that such peptides will have no effect on muscle tissue and that they are just not suited for use in the comparatively active site of heart muscle compared to brain tissue. There are many other factors that may mean that use in the heart is not possible. As stated, one possible factor that may limit or stop the treatment would be that in order to form a scaffold that will be sufficient to allow tissue to form the peptide nanorods need a much stiller environment, not one that is moving twenty four hours a day. Another factor may be that the environment within the pericardial sac is not suitable perhaps due to pH or temperature. Finally, as muscle fibre is completely different to brain tissue it may respond in a completely different manner and may not bind to the peptides or may even have an adverse reaction to their presence. However, with modern science being as advanced as it is, there should be many a solution to the problems presented, especially when working at an atomic level, the smallest of things can be changed allowing for great manipulation of materials. This would most likely allow for a very complimentary material to be developed, one which would hopefully have no negative effects on the body.

The breakdown of peptides;

The final issue to confront is that of the safe removal of the peptides from the body. It would be highly beneficial if the peptides were broken down into harmless polypeptides that could easily pass into the blood stream and be filtered out of the body by the kidneys and excreted in the urine as was shown in the hamsters. It is imperative that the peptides should not have any extreme affects upon the liver or kidneys so that they can be given across a much broader spectrum of patients. However, if they did then measures and

guidelines would be put in place to restrict their use to allow for public safety and protection.

To conclude, these nanomolecules are not new, they have always existed, our biggest challenge as a race determined to push the boundaries of science is to adapt and build new technologies to do things to atoms and molecules that nature has been doing unassisted for millions of years- to build them for a specific job.

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