Potential applications of plasmon-active gold nanoparticles in medical treatments

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PASS

Abstract

The big problems with most conventional methods of treating disease currently are that they can be intrusive into the body e.g. to remove a tumour, and they are often indiscriminate and unspecific. These limitations increase the risk of infection and also increase the cost to medical service providers because large amounts of medicine are required to fight infections or cancers. This paper looks into the potential use of plasmon-active gold nanoparticles as drug delivery systems and as treatments themselves. It examines the possible alternatives, and identifies ethical issues involved with these methods of treatment.

Introduction

Nanotechnology is one of the newest areas of science and there is a lot still to be explored within the field. Nanotechnology is defined as the study and manipulation of molecules and structures with dimensions less than 100nm; or 10^{-7}m which is about a thousand times thinner than a human hair. Richard Feynman, who is largely heralded as the father of nanotechnology, once described the scale of nanotechnology by saying that if you wrote '*How is this?*' onto a piece of paper as small as you could, then someone else would be able to write *'Not so hot'* onto the dot of the 'i'.

However, even though nanotechnology is a new area of science, nanoparticles are not a new thing. Buckminster fullerene (a carbon allotrope of nanometre dimensions) for example is produced in small quantities when carbon compounds are burnt. Buckminster fullerene has also been found in deep ice over the Arctic.

One of the many fields that nanotechnology is making major advancements in is the field of medicine. Current medical treatments are usually indiscriminate and affect healthy body cells as well as the damaged or pathogenic cells, either because surgery is required or because the drugs given have no way of distinguishing between body cells and harmful cells. If surgery is required then the risk of infection is increased and other complications may arise. Other treatments such as chemotherapy for cancer and antibiotics for infections can cause side effects and cause damage to healthy cells.

Applications of nanotechnology in medicine that have already been explored are methods of sensing and diagnostics within the body, methods of injecting drugs into the body without any risk of infection and methods of treating cancer directly. Nanoparticles make good diagnostic tools because they can reach lots of places within the body easily through the blood stream and are also very sensitive due to the size. These usually take the form of carbon nanotube field effect transistors (CNFETs) which can detect very small changes in the environment when a biological functional group is bonded to the carbon nanotube, which controls the resistance of the nanotube. Nanostructures have also provided an infection free method of injecting drugs into the body. This is because the nanotubes have such a small diameter that the hole made in the patient's skin is much smaller than the width of a pathogen. Nanoparticles are now starting to be used as drugs themselves for similar reasons. The tiny size of nanoparticles means they can access every cell in the human body through the blood stream, and the ability for nanoparticles to recognise their target cells as well as treat the cells makes them a more efficient method of treatment. It is into this category that plasmon active gold nanoparticles (PAGNs) fall.

Discussion

PAGNs are nanoparticles made with gold atoms in various structures; usually gold nanospheres or gold nanorods. Gold has several different properties which make it the material of choice for nanotechnicians; it is very unreactive, ligands can be attached and the metallic bonding allows electrons to move.

The use of gold nanoparticles is quite a new field and the closest current equivalent is photoactive dyes. These dyes are injected into the body and usually have certain properties which make sure they only dye the desired tissue. These dyes are then activated by carefully selected wavelengths of light so that they radiate heat and therefore kill the tissue they have dyed. A big downside of these dyes is that they tend to be quite large, complex molecules with a small surface area to volume ratio. Gold nanoparticles on the other hand are made into nanospheres or nanorods which have a large surface area to volume ratio and so have much higher absorption efficiencies. Gold nanoparticles are also useful because they are very unreactive and therefore are unlikely to cause any other damage to healthy body cells. The third characteristic which makes gold nanoparticles so suitable is the fact that using sulphur-gold dative covalent bonds you can attach organic molecules to the gold nanoparticles, such as a monoclonal antibody (an antibody which binds to the antigen on a specific kind of cell) which enables the scientists to manufacture drugs which recognise the target cells, see Fig. 1.

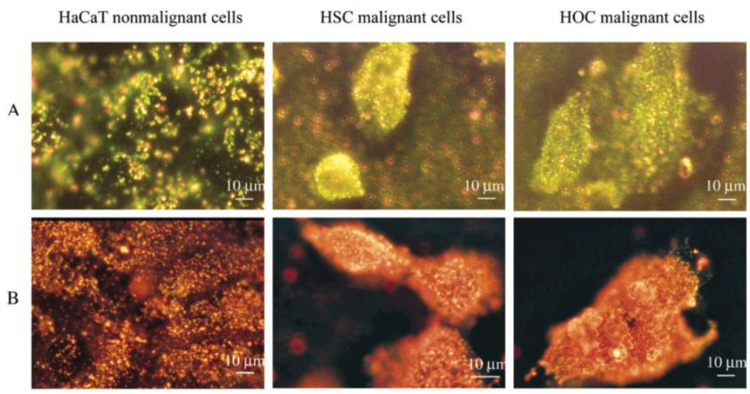

Figure 1

The final characteristic which makes gold nanoparticles useful is the fact that they can be plasmonically activated. If a molecule is plasmon-active it means that when it is irradiated with different wavelengths of light the molecule will vibrate at the same frequency as that of the light thereby converting light energy into thermal energy. Gold is plasmon active because it forms metallic bonds, therefore meaning the electrons are delocalised; this means that as the radiation is absorbed by the gold particles the electrons in oscillate between the top surface and bottom surface (relative to wave) thereby converting light energy into thermal energy, see Fig. 2. Gold as a metal requires wavelengths in the visible part of the electromagnetic spectrum, wavelengths of about 520nm in length which correspond to green light. However when the gold nanospheres and nanorods (absorption is dependent on aspect ratio for nanorods) are produced they have different resonances due to the fact that the light is absorbed and emitted by multiple surfaces and therefore is red shifted into the infrared region of the EM spectrum. This is a useful characteristic because unlike visible light, infrared can travel through human skin to a certain extent, allowing the drugs to be activated inside the body. Nanorods especially increase the absorption efficiency as they have 2 absorption peaks due to the 2 different shapes of surface (curved and flat).

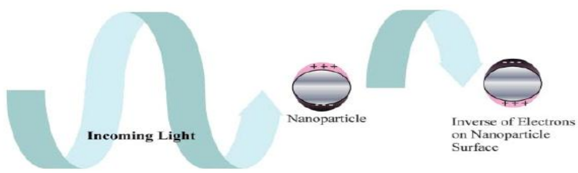

Figure 2

The fact that PAGNs can convert light into heat has allowed two methods of treatment to be developed; drug delivery systems and localised heating. PAGNs can be used as drug delivery systems because the desired drug can be encapsulated or bonded to the nanoparticle in such a way that when the PAGNs are irradiated with infrared light and the heat is emitted, the respective drugs are released into the surrounding area. This is advantageous over existing treatments because it allows the relevant drugs to be administered directly to the desired area e.g. to the cancer cells in a tumour or to the bacterial cells in an infection rather than generally administered into the bloodstream in the local area. This in turn means that smaller quantities of drugs can be used, as all of the drug will make it to the relevant areas and will be more effectively administered, reducing the cost to health services. Also, the nature of this treatment means it can be used alongside most drug related treatments such as chemotherapy for cancers or antibiotics for pathogenic infections; this is not a treatment to supersede drug treatments, just an advancement to improve the way drugs are administered. Localised heating isn't a new treatment either; localised heating has been used to burn away benign moles with lasers, for example. The only difference in this case is that it can be effectively done, deep inside the body. This type of treatment would involve the PAGNs bonding to the target cells using monoclonal antibodies and then releasing concentrated amounts of thermal energy to the surrounding area when irradiated with the infrared light. This heat denatures enzymes and damages structures within the cell resulting in the death of the cell. The advantage of this method over drug based treatments is that the PAGNs aren't 'used up'; they can move onto other cells and kill those as well after the death of their current cell. This can effectively kill any tissue so desired. The fact that the cells emit heat into such a small local radius will also limit the amount of heat generated so as to limit the damage caused to healthy cells however will still be effective because of the number of PAGNs surrounding the tissue to be destroyed.

However there are several issues with the use of PAGNs of various forms. Medically, there is a relatively high risk associated with using PAGNs and so special care must be taken. Because PAGNs are activated by infrared radiation the patient must be exposed to the infrared radiation during treatment. Infrared is by no means the most dangerous kind of electromagnetic radiation that a patient could be exposed to but it can still pose dangers if care isn't taken. The power of the light source used to irradiate the patient must be kept low so as to keep the amount of energy in the wave low. The PAGNs have a minimum power of light to activate and work effectively (80mW), but past 120mW and the radiation starts to damage healthy cells as well so the radiation has to be kept within safe levels, see fig. 3. This means that staff will have to have extra training in order to be able to use the equipment safely and therefore avoid causing unintended damage to the patient. This along with the fact that new equipment would have to be bought and maintained means that these methods of treatments will pose extra costs for health services. Equally there is still the same risk of infection when injecting the PAGNs into the body as these particular methods do nothing to prevent this although other areas of nanotechnology are making advancements in this field.

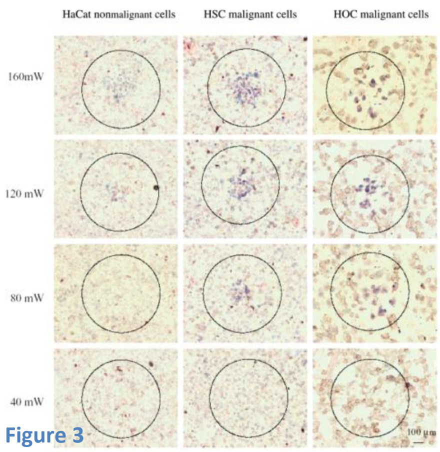

Figure 3

There are also a number of post-treatment concerns that present themselves. Can these particles cause any side effects? Is the body able to process and remove them after the treatment is complete? Is there any possibility of these particles being activated by background radiation in an uncontrolled environment after treatment is complete? As far as side effects go, there isn't any definitive studies into what side effects could be caused in humans as the treatments haven't been fully tested yet; however it is thought that they will cause fewer side effects than current treatments. The main problem here is that the PAGNs are susceptible to being fought by the body's own defence mechanisms so without devising a way to access the target area without triggering a humoral or cell mediated response. I would expect the side effects in this instance to be similar to that of vaccinations as the body tries to fight the "infection" of PAGNs. Again the research is still being carried out but studies performed on mice suggest that the kidneys are able to process and remove the PAGNs from the body. The possibility of PAGNs being activated inside the body by background radiation is fairly small as the amount of background radiation of the right wavelength is quite small and isn't enough to penetrate the skin of the body and still have enough energy to activate the PAGNs. However once the body processes them and removes them from the bodies system and the particles are in the general atmosphere there wouldn't be any barriers between the particles and the radiation and it is entirely possible that the PAGNs could be activated once in the atmosphere.

There are also environmental concerns about nanoparticles. One big problem with nanotechnology at the moment is that there is currently a lot of research going into producing new nanostructures, but not so much research going into the environmental effects of these nanoparticles. This means that the environmental effects are not currently fully understood and only recently have governments and other organisations really begun some co-ordinated research. Some issues that have arisen are: Do these nanoparticles break down? What happens to them after they leave the human body? What effects do they have on the ecosystems they could infiltrate? PAGNs don't break down very easily as there aren't any organisms with the enzymes to break down these particles. So after they leave the human body these particles will enter sewage systems and ultimately enter into water sources. This makes it likely that they would come into the category of pollutant known as PM<10 or particulate matter, which is the term given mainly to small particles of carbon that are released in combustion. So as the concentration of nanoparticles in the atmosphere increases they may start to cause lung problems, having a similar effect as PM<10 or asbestos fibres. This would be exacerbated with PAGNs because once in the lungs there would be the risk of them activating and releasing heat to the surrounding lung tissue. These particles could also go through a similar process as pesticides and fertilisers and end up in water sources. Potentially, large concentrations of PAGNs in water sources could raise the average temperature of these water sources, which could cause a number of changes in these ecosystems. This problem could also present itself as a greenhouse 'gas'; a greenhouse gas being defined as a gas which absorbs infrared radiation and converts it into thermal energy in the atmosphere rather than letting the radiation pass straight through. So these particles could also contribute to global warming if suitable mechanisms and legislation aren't put into place. On the other hand a lot of these undesirable effects will only come about if the concentration of these particles in the environment reaches high levels, which is unlikely but should also be controlled by governments around the world.

As for the future applications of PAGNs it is thought that they could be combined with gene therapies in order to further enhance the treatments that could be offered. Currently any future research into PAGNs will be with the aim of developing them and rigorously testing them to make them suitable for human treatments. Once the PAGNs have been completely developed and tested it is likely that only those patients where conventional methods would be unsuitable will be offered this new treatment until such time as it can be proved to benefit the welfare of the patients and to be cost effective.

There doesn’t appear to be much research on the subject but it appears to me that there could be uses of these particles as contraceptives as well which could replace the morning-after pill as the PAGNs could identify early embryonic cells and/or gametes and kill these cells to prevent a baby growing. This would bring with it its own set of ethical issues but they would only be the same ethical issues already raised about current contraceptives. Another possible application the presents itself is for PAGNs to repair tissues. Coupled with stem cell research it could remove scar tissue on the liver for example by removing the scar tissue through localised heat bursts and replacing the removed cells with stem cells which could grow into healthy liver tissue. Another potential treatment could be to treat paralysis due to neck or back injuries. This is thought to be caused in some cases because the myelin sheath has been damaged and so no longer insulates the nerves at long the spinal column. PAGNs could carry the materials necessary to replace the myelin sheath and when it identified a nerve cell with damage to its myelin sheath it could be activated and could replace the insulation around the damaged axon, hopefully restoring motor control.

The potential for PAGNs is extremely varied and I have come up with only a few ideas. It seems to me that the potential for PAGNs is limited only be the imagination of the scientists creating them as they have such versatile characteristics in terms of transport mechanisms and in terms of direct treatments.

Conclusion

Nanoparticles are small particles with diameters smaller than 100nm and have many applications in this world, a large number of which are medical. One such medical application is the use of functionalised plasmon active gold nanoparticles to treat damaged or unwanted cells in the body. Due to their size PAGNs can access any cell in the body and with monoclonal antibodies can target any kind of cell desired. Once they have identified the target cell and the concentration of PAGNs is sufficient to cause the desired effect the particles can be activated by bursts of infrared radiation which will be converted into thermal energy which will be concentrated around the cells the treatment is trying to eradicate thereby killing the cells and causing little damage to the cells of the body.

PAGNs are theoretically better and more efficient than their current counterparts – photoactive dyes. This is because the surface effects of PAGNs allow much higher absorption efficiencies than photoactive dyes. PAGNs are also much easier to functionalise because it is easy to attach ligands through π-π stacking which allows biologically functional groups such as antibodies to be attached. This allows for greater specificity and active targeting of cells.

PAGNs are currently being developed as a method of treating cancer either by delivering drugs to the specific site of the cancer or by killing the cells with heat converted from infrared radiation. Currently the tests have only been performed on mice but future research will identify any problems with the techniques and make them suitable for human use. These particular techniques can also be combined with other techniques to make them more effective or more efficient.

PAGNs are activated by irradiating the body with infrared radiation with a power between 80mW and 120mW. This allows the PAGNs to be activated without causing damage to the tissue in the body. Also due to this being a relatively high value in comparison to the background infrared radiation, there is little risk of PAGNs being activated outside of treatment. However they may still be activated once outside of the body.

PAGNs have many ethical issues including religious, environmental, medical and economical. Future developments may reduce these issues but may bring up new ones. At the moment the aims are to develop active targeting techniques which can evade the immune system and also to test and research these treatments to ensure the safety and wellbeing of the patients. Some governments along with several non-government organisations, including Greenpeace and the EPA, are now conducting research into the environmental aspects of nanotechnology with the aim to determining what concentration of nanoparticles would be dangerous to humans and also to the rest of the environment. This research will be the basis of legislation in future years to control the manufacture of nanoparticles.

Future applications include gene therapies, contraceptives, treatments for repairing damage, and any other treatment that requires any specificity. Due to the fact that PAGNs can recognise cells and deliver any type of drug they will be able to combine with any other drug related products and may also be used to ‘deliver’ and activate nano-machines. Some problems with these future developments may be that self-assembling molecules (SAMs) may become out of control if introduced to the body and nano-machines can be difficult to halt once the process is complete.

In general, the future of PAGNs is bright, albeit with a lot of research and ethical barriers to come. The versatility of these molecules makes them ideal for advancing almost any area of medicine including diagnostics, treatment and drug delivery. They may also reduce costs for health services due to their efficiency, and high demand for new technologies. I expect to see PAGNs forming the basis for many treatments in the future along with many other areas of nanotechnology.

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