CURING PARKINSON'S DISEASE AND IMPROVING INTELLIGENCE, COULD THIS BE OUR FUTURE THROUGH EMBRYONIC STEM CELL RESEARCH?

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Abstract

Embryonic stem cells are a potential future development that is widely recognised due to the pluripotent nature of the cells. Much research is being conducted at the moment to suggest that in the future, the effects of Parkinson's can be completely reversed. Replacing the lost dopamine producing neural cells in the substantia nigra with the correctly functioning stem cells would achieve this. Furthermore, we believe that the same treatment could possibly be used to increase concentration and alertness in healthy people. We have found that there are a few problems that will need to be overcome in order to achieve this such as the development of tumours, rejection by the immune system and controversial ethical considerations.

Introduction

Stem cells are unspecialised cells with the potential to differentiate into other types of cells. When a stem cell divides, it creates one new stem cell and one precursor cell, which divides again and again until it becomes specialised, meaning it is a specific cell such as a red blood cell. Some stem cells can only differentiate into one type of cell (unipotent), a few types of cells (oligopotent) or multiple cells (multipotent). These are usually adult stem cells. Embryonic stem cells are usually pluripotent meaning they can differentiate into almost all cell types and the cells that result from egg fertilisation are totipotent meaning they can develop into any type of cell.

For this reason, there is a great amount of research currently being undertaken into the development of stem cells in providing treatments and cures for a wide range of conditions and diseases. The idea is that if we can guide and determine the type of cell that these stem cells differentiate into, we could potentially use them to grow cultures of specialised cells that could be used within medicine. The majority of research is being undertaken into the development of embryonic stem cells due to their ability to differentiate into almost any other cell. The importance of these stem cells to medicine is that they could be vital in tissue repair and regeneration. They could potentially be used to grow skin cultures to be grafted back onto the skin in the case of burn victims, replace damaged spinal cells in breaks of the spinal cord, repair damaged heart muscle and possibly even grow whole new organs for transpants.

Embryonic stem cells are extracted from embryos developed in an in vitro fertilisation clinic with eggs donated for research purposes. The balls of embryonic stem cells are usually 4 or 5 days old and known as a blastocyst. The inner cell mass is a group of approximately 30 cells. This mass is then transferred to a culture dish containing nutrients where they are encouraged to replicate. When there are too many cells within this culture dish, they are moved to a new one where they can divide again to produce more pluripotent cells.

Discussion

Parkinson's sufferers have a loss of nerve cells in the subtantia nigra, cells here generate dopamine; dopamine transmits messages to other parts of the brain that co-ordinate movement. Therefore Parkinson's often affects movement such as walking, talking and writing. This is because without these dopamine producing nerve cells,

messages cannot be sent to the parts of the brain co-ordinating movement. When about 80% of the dopamine producing cells has been lost, the symptoms of Parkinson's appear and since the disease is degenerative, the number of dopamine producing cells continues to fall over time.

We were inspired to write about this particular topic because we have strong connections with the diseases. Our first instinct was to research MS and Parkinson's as both of us have close family members, one whom died whilst suffering with Parkinson's and one close family member who is currently suffering from MS; however whilst doing the research we became mainly interested in Parkinson's and decided to focus on this particular area. We also believe the future development into stem cell research linked with Parkinson's is promising and the possibilities could revolutionise medicine.

There are many treatments available at the moment for Parkinson's, however; these generally treat the effects rather than the cause of the disease. In addition to this, none of them work perfectly and so far no cure has been developed for Parkinson's. The first is drug treatments that hope to increase the amount of dopamine that reaches the brain, stimulate the dopamine producing nerve cells and block any hormones and enzymes that reduce the effects of dopamine. The next is therapies such as occupational therapy and physiotherapy with some, but little substantial effect. The final is surgery that inserts electrodes into the brain that stop or reduce the symptoms of Parkinson's. As these all treat the symptoms rather than the cause of Parkinson's, an enormous amount of research into the disease and alternative treatments is currently being undertaken. The treatment considered one of the most prospective and with the most potential is the use of embryonic stem cells.

If we could develop cells that can replicate the existing cells, have the right DNA and not contain the antigens that activate the immune system to attack then possibly we could re create the brain without any fault. Sufferers of Parkinson's may be cured or at least given an alternative and a better standard of life. If we could produce stem cells that can be specialised into the specific neurones that produce dopamine then we could replace damaged neurone and the problem is solved. In spite of this simple solution, it is not simple at all; it's quite the opposite. Making the cell follow the correct information in the DNA to make one extremely specific nerve cell is difficult. However Scientists have been able to produce the nerve cell but its life span is not long and is found to die after transplantation.

Although, this treatment using embryonic stem cells isn't available at the moment, it is a serious prospect for the future and one that whilst research is being done it is becoming closer and closer to being accomplished. Such research is providing copious amounts of hope for sufferers of Parkinson's and their families. Research into regenerative treatment of Parkinson's was started over a decade ago. Research by Hauser (1999) was one of the first trials with fetal nigral neurons (the dopamine producing cells that are destroyed in Parkinson sufferers) where these cells were implanted into the correct area of the brain. Six patients with advanced Parkinson's disorder were given grafts of cells extracted from 6.5 – 9 week old foetus's, with cyclosporine to suppress the immune system. Studies on the patients were followed up for 24 months afterwards on the 4 of the patients who survived and found an

increase from 22% to 60% in the time they were without dyskinesia (involuntary movements often caused due to treatments for Parkinson's). These studies showed an increase in motor functions, which correlated with clinical improvement. Unfortunately, no benefits were shown in the double-blind trials of this treatment. Therefore, research into fetal cells is no longer being undertaken.

Instead, a lot of research is currently being undertaken into embryonic stem cells (ES cells), which are believed to have a greater chance of success due to their pluripotent nature making them more versatile and hopefully easier to differentiate into specific stem cells. ES cells were first isolated by James Thompson in 1998 and over the last decade, have been studied extensively in attempts to harness them for use in medicine. Likewise, mouse embryonic stem cells have also been researched into during the last 20 years and it is know that when placed in culture, these ES cells become embryoid bodies displaying characteristics of the three layers of the embryo: endoderm, mesoderm and ectoderm. These layers give rise to being differentiated into many different types of cells. Luckily, it has been found that human ES cells behave in exactly the same way as these mouse ES cells whereas primate ES cells have not been found to be cultured into embryoid bodies.

Research by Professor Benvenisty (2001) has shown that by treating human ES cells with nerve growth factor or retinoic acid has produced 50% of cells that are capable of forming neural networks and therefore could be transplanted into the brain to become neural cells. It would therefore seem simple that we could treat the ES cells with this nerve growth factor, which would trigger the cells to differentiate into neural networks that could be transplanted into the substantia nigra, produce dopamine and reverse the effects of Parkinson's. However, there is one problem that must be overcome in order to achieve this; it has been spotted through research with mice and is the production of tumours known as teratoma within the brain. Research by Dihne (2006) has shown that 70% of mice that receive ES cell derived neural precursor cells develop teratomas. Assuming similar results would be gained using human ES cells, this is far from a perfect solution. The same research also shows that a way of reducing the risk of developing teratomas is by using more mature cells that have become late neural precursor cells rather than transplanting them as undifferentiated cells. It is foreseeable that using this information, research can provide an answer to the most suitable stage of maturity within the cells and this information used to overcome the issue of resulting teratomas.

Another problem with ES cell regeneration is rejection by the immune system. ES cells are susceptible to rejection in the same way as organ transplants can be rejected. Organ transplant drugs such as cyclosporine and the ones used in chemotherapy can suppress the immune system and delay the body from rejecting the cells. However, this does not have a good effect on the patient and is not proven to completely prevent rejection. Fortunately there are some possible solutions to this problem; the first is to use embryonic stem cells by creating embryos from the DNA of the sufferer. Although with Parkinson's, this would generally not be possible as the disease usually affects people over the age of 50 who would, women in particular, generally not be able to produce the sex cells needed to create the embryo. The next solution is that although ES cells are susceptible to rejection, research by Dr Fairchild who is working on overcoming this issue, shows that they may have the potential to prevent rejection themselves. Dr Fairchild at Oxford University has discovered that ES cells

contain potential immune privilege that may be harnessed therapeutically to prevent rejection. He is also conducting research into whether viruses and tumours could potentially exploit this privilege and use it to their advantage. However, this is a very exciting development and almost moves us one step closer to the successful use of embryonic stem cells in medicine. With further research into immunity, we could find a way to make all ES cells immune to rejection and by inserting them in a more mature state, potentially eliminate a large amount of the risk of failure that exists in the theory of transplanting embryonic stem cells today.

Future developments

Following this research, we are lead on to discuss our ideas for the future developments that could be achieved by using the treatments that are being studied and hopefully will be perfected in the future. Our idea is that the effects of Parkinson's could be completely reversed owing to the transplant of dopamine producing neural stem cells. Patients with Parkinson's would be diagnosed as they started to show symptoms of the disease and it would therefore be discovered that 80% of the dopamine producing cells would have been lost. Nowadays this would be the onset of a chronic and progressive disease but in the future, treatment could be started straight away to reduce the symptoms, replace the lost stem cells and allow the patients to continue with their life as before. Some types of Parkinson's disease can be hereditary with an increased chance of 2-5% if a close relative also has the disease. In addition, some cases have a known mutation in the Parkin gene, which is also inherited and in these situations, the relatives would be able to be tested for the disease much sooner. They could then be diagnosed earlier than the 80% loss of cells that generally causes the onset of symptoms of the disease. This would mean that fewer new stem cells would need to be added to replace a lower proportion of lost cells.

Within this treatment for the future, scientists would take embryos and extract the ES cells from them. They would then grow them in culture, treat them with nerve growth factor, which would encourage them to become neural cells and allow them to divide. As they divided, scientists would take the precursor cells that showed neural characteristics to be transplanted into the brain. The immune privilege would also be harnessed therapeutically, as is being researched currently, so that once the cells were implanted, they were not rejected by the body as they proved resistant and managed to adapt to the environment they were inserted into so that the immune system did not recognise them as foreign. They would then be transplanted into the body where they would be instructed in their DNA to grow taxons and therefore connect with the correct parts of the brain to form new networks. This would be achieved by mimicking the work by Björklund *et al* who used mouse ES cells to preserve the phenotype of the cells along with ensuring that neurites can connect with the correct target cells along with having 56% of the animals that didn't develop tumours. This is very promising and could therefore be applied to human patients suffering from Parkinson's disease in the future. Kawasaki *et al* also managed to treat their cells with mitotic inhibitors to prevent the formation of a tumour. These are methods with much potential that will clearly be able to be perfected in the future.

Taking these developments further, it is clear to see how this very same method could be used to benefit people in the future in slightly more unconventional ways. If we can help people suffering with Parkinson's and recreate the nerve cells that produce dopamine perhaps this is a pathway into more controversial uses of the techniques.

There is a drug called Ritalin that doctors are prescribing to children who are suffering from attention deficit hyperactivity disorder (ADHD); this drug stimulates the brain to produce certain chemicals and hormones including dopamine and noradrenalin. The drug is prescribed to calm the child down and help them concentrate; Dopamine is the same hormone scientists are trying to manipulate stem cells into nerve cells to secrete. Ritalin is also being bought off the internet and people believe it to be a drug that stimulates the brain. If you do not suffer from ADHD then by taking the drug it has the effect of making you more alert and helps you concentrate.

Potentially we could help people who are not ill; we could improve their alertness and help them concentrate more by transplanting the dopamine producing nerve cells into their brain. With this increase in concentration for a longer period of time, more information will be put into the long-term memory and therefore people would become more intelligent as they could recall a lot more information. Even further into the future we may be able to concentrate on techniques of improving the brain and intelligence of our species. This is perhaps an unethical pathway.

The Multi-store model of memory which was first discovered by Atkinson and Shiffrin in 1968 is a way psychologists believe the memory works; it's a basic idea and there is evidence to support it. It works in three simple stages, sensory, short term and long term. Sensory is where we store information for a few seconds, information such as fragrances or sounds, things we pick up though our senses. However if the information is not of use to us it decays. In the short-term stage information that is slightly more useful is retained between fifteen and thirty seconds until it decays and if it is rehearsed it enters the long-term memory. In the long term memory it is believed information is for an extremely long time; the problem is accessing it and there are also theories of trace decay. Previous case studies have shown that if one of the stores/stages is damaged then it blocks the gateway to other and that person's memory is damaged. If we can re-connect areas of the brain, transplant nerves that secrete memory stimulating hormones and open new gateways to each memory store then perhaps we could make the perfect memory.

There are many ethical implications of stem cell research; particularly the uses of embryonic stem cells, they are causing controversy between scientists, religions and politicians. Scientists believe that with the use of embryonic stem cells they could cure and relive many people who suffer daily and those who die from what is potentially is a curable disease. Scientists need to do the research to save lives. On the other hand is it justifiable to take one life and use it to save another? On the contrary is it justifiable to take a life through an abortion and cast it aside; therefore is it not fair to use this unwanted life as a way of potentially saving others? If on reasonable grounds a young woman wants an abortion, she should have the right to donate the umbilical cord.

Many religious leaders believe it is not right to "murder" a potential life; should we as humans play god? Many beliefs do not believe in abortions such as the Catholic Church; abortion is evil and a form of murder. Therefore using the embryonic stem cells from an unborn child is wrong. Some religions believe experimenting on parts of a "murdered" child is not the way in which we should behave as humans and is completely unethical. Politicians are having difficulties on what to do and whom to please; if upsetting people is going to save lives, is it the right thing to? In recent news the president Barack Obama lifted restrictions and gave the support needed for embryonic stem cell research in the US. If such an influential man can give this support then perhaps he can give motivate other to support the cause. In spite of this, scientists are still playing God by altering our genes and by recreating new humans; religions may be critical of this too.

The drug Ritalin, which is use to calm sufferers of ADHD, has had improper use when students have used it to keep them more alert and to help them concentrate more. But can this really be cheating? All it is doing is making them more motivated rather than them getting fed up and having to rest in between revision. So the ethical arguments that are consequence of using this drug to stimulate the mind could be the same arguments considered with using the nerves cells to stimulate the mind. People see improving the memory as cheating from what we are naturally capable of. If an athlete use drugs to enhance his performance and suffers from doing so; using dopamine producing nerve cells to help improve our minds could also been seen as cheating.

Conclusion

On the whole we believe that if the right techniques have been produced then not before long future nerve cell transplants will productively be taking place; Parkinson's symptoms won't just be what has been treated but the illness itself may become extinct; in that sufferers can live an almost normal life without being frightened or concerned about their health. Further development into the ideas of nerve cell transplants that improve memory can lead to transplants in perfectly healthy brains so they have more intelligence. It could be as a form of cosmetic surgery; and help us grow into better individuals being more alert and able to learn. Some of these ideas may have controversial effects and cause arguments between races and individuals but if it saves lives and if one day it can be accepted then we believe it's a risk worth taking.

However we have also discovered that there are many problems that need to be overcome in order to make our ideas a reality. This is the reason behind these treatments not being available at the moment as it is clear that there is a copious amount of research being undertaken in these areas. As we have mentioned earlier, these are the possibility of the development of tumours occurring after the transplantation and also the danger of rejection of the transplanted embryonic stem cells by the immune system. There are current research projects that suggest that differentiating the cells before inserting them into the body and harnessing their immune privileges will be able to solve these problems however they are far from being perfected solutions but hold much hope for the future. The other potential downfalls are the ethical and controversial implications of this type of treatments as

described earlier. Many people are against this type of treatment due to its involvement with the destruction of embryos which many consider potential lives. Therefore, scientists are also conducting vast amounts of research into alternative uses of non-embryonic stem cells that could be harnessed to produce the same results. Scientist are trying to overcome these problems everyday and with president Barack Obama funding stem cell research the reality of curing or preventing these illnesses can and will be possible.

In 2007 scientists founded a new technique of recreating a cell that behaved like an embryonic stem cell. By using viruses to genetically modify the cells there were able to recreate the Pluripotent behaving cells from fibroblast skin cells; however the researchers believed the cells had a risk of becoming cancerous and therefore they could not be used in medicine. In addition, it has recently been discovered that they can now do it without using viruses; by using foreign genes to reprogramme the cells they appear to not be cancerous. Religious leaders cannot argue that lives are being "murdered", scientists can continue to research without upsetting others and politicians can have the satisfaction of pleasing everyone.

Furthermore when these procedures are available will they be economic? Are they going to be extremely expensive and only be available to those with the right income? Will they only be available for the higher class; making working class and those further down the ladder fall even further behind in society and giving the richer a head start as they have been "man made" to be more "intelligent"!

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