Pearson Edexcel International Advanced Level

Biology

Advanced

Unit 5: Energy, Exercise and Coordination

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Scientific Article for use with Question 7

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Scientific article for use with Question 7

Chasing the cure: A decade of Parkinson's Disease

Decade of Advances in Parkinson's Disease Research

1. "What's happening in research on Parkinson's disease (PD)?" This question is always uppermost on the minds of people with Parkinson's and their family members. To answer it, I have looked back at the research conducted in the past decade or so. It turns out that between 1997 and 2007, more than 23,000 scientific articles addressing Parkinson's were published.

2. This large number reflects the excitement stirring in this field. But what did the research yield? While we have much further to go in our understanding of Parkinson's disease and towards our goal of finding a cure, I expect that you will be as impressed as I am by the serious investment of time and resources that is going into this important research.

Genetic and Environmental Causes of PD

3. To me, the most exciting and important area of PD research during this period is genetics. Although few cases of Parkinson's disease can be attributed to genes alone, identifying the types of genetic mutations that lead to PD has given researchers tools for unraveling the molecular mechanisms that underlie the disease.

4. In 1997, scientists described the first gene known to be mutated, or changed, in PD. The gene named SNCA, or PARK1 (the first in a series of PARK genes that now number more than a dozen) codes for alpha-synuclein, a protein that we have since learned may play a very important role in the development of PD. While mutations in this gene are very rare, the discovery that an alteration of alpha-synuclein is involved in PD spurred researchers to study it. They found that this protein is present in the Lewy body, a foreign inclusion in neurons that is the pathologic hallmark for PD.

5. Another important genetic discovery related to alpha-synuclein was that the mutation known as PARK4 was actually a triplication of the normal SNCA gene, meaning that people with PARK4 had extra copies of the gene and thus, an excess of normal alpha-synuclein. So, too much alpha-synuclein – and not just an abnormal form of the protein – can cause Parkinson's, albeit in very few people. Partly because of this discovery, much research in the last decade has focused at the molecular level on the mechanisms by which the alpha-synuclein protein contributes to the death of dopamine neurons. It is now understood as one of three elements within the dopamine neuron – the other two are dopamine and calcium – that interact to cause neurodegeneration.

6. There are several other genes that have been implicated in PD. Some rare mutations are implicated in the onset of PD at a young age, usually before the age of 30; these genes are PARK2, PARK6 and PARK7. Their abnormal gene products appear to affect the function of the energy factory of the cell – the mitochondrion.

7. The most common mutations that contribute to Parkinson's occur in the gene known as PARK8 or LRRK2. Mutations in many different parts of this gene have been discovered, and they can occur in people who do not have a family history of PD. In fact, mutations in this gene have been identified in more than two percent of people with Parkinson's in North America and England, who do not have a family history of the disease. They are found even more frequently among people with Parkinson's disease who are of Portuguese, Spanish, Ashkenazi Jewish and North African descent. It is not yet understood how the abnormal LRRK2 protein causes PD. This should be an area of intense research in the future.

8. Since Parkinson's usually cannot be attributed entirely to genetics, scientists have also studied environmental contributions. A large study of identical twins in which at least one member of the pair was diagnosed with PD helped to sort out the relative genetic and environmental contributions. The researchers found that when PD was diagnosed before the age of 50, it was much more likely to have a strong genetic component than when it was diagnosed later in life.

9. Environmental toxins have long been considered a potential trigger for PD and much research has focused on pesticides. From research on laboratory animals and also from studies that collected data on large numbers of people who were exposed to pesticides (known as epidemiological studies), we have learned that the chemicals rotenone and paraquat contribute to PD. But the relationship of pesticide exposure to Parkinson's remains unresolved, and the search for an explanation continues.

10. Scientists are also investigating whether an underlying genetic predisposition could combine with pesticide exposure to result in PD. In the meantime, some things in the environment have been shown to correlate with a lower risk of Parkinson's. Smoking cigarettes is one (although it can lead to other health problems); others are drinking coffee, having higher levels of uric acid in the bloodstream, and having gout.

How PD Begins: A New Theory

11. We have long known that the motor symptoms of Parkinson's begin when dopamine-producing cells die in a part of the brain called the substantia nigra. This is often the point at which people with Parkinson's first receive a diagnosis. Then, along came a theory suggesting that at this point, people are already at a relatively advanced stage of the disease, and that PD actually starts earlier, with changes in other areas of the brain and elsewhere in the body.

12. The theory was first proposed a few years ago by the German researcher Heiko Braak, M.D. He and his colleagues examined the autopsied brains of people who had died with Parkinson's and found that alpha-synuclein protein accumulated in areas other than the substantia nigra. These areas, including the pons and the medulla in the brainstem, control body functions such as digestion, heartbeat and the regulation of sleep. His team also found widespread deposits of alpha-synuclein in nerve cells in the gut.

13. These discoveries led Dr. Braak to propose that alpha-synuclein abnormalities begin to accumulate in "lower" regions of the nervous system, eventually reaching "higher" areas in the brain. Dr. Braak's hypothesis has stimulated much discussion and debate among researchers. His observations may explain some of the nonmotor symptoms of PD, such as constipation, changes in sleep and mood and decreased sense of smell.

14. Beyond noting accumulations of alpha-synuclein, new research has shed light on other molecular mechanisms by which neurons degenerate in PD, including oxidative stress, alteration of the mitochondria and inflammation. The understanding of these processes has led to new ideas for developing therapies for Parkinson's.

Diagnosing Parkinson's and Measuring Its Progression

15. Partly because of Dr. Braak's hypothesis, researchers are searching for biomarkers to detect PD before the motor symptoms become manifest.

16. One method that has shown promise is neuroimaging – that is, getting a picture of the brain using techniques known as positron emission tomography (PET) and single photon emission computed tomography (SPECT). In clinical trials evaluating people newly diagnosed with PD that also included one of these imaging techniques, ten to 15 percent of these individuals had scans without evidence of a dopaminergic deficit – meaning they did not have PD at all and there was some other cause of their tremor and slowness. These individuals did not respond to levodopa therapy. Some PET techniques have been helpful in differentiating PD from atypical parkinsonisms, such as multiple system atrophy and progressive supranuclear palsy. Such tools could be helpful in both diagnosing PD and treating it earlier in its progression.

Findings in the Clinic

17. James Parkinson's original description of PD stated that the "senses and intellects" were "uninjured" in the disease. But we have known for many years that this is not the case, possibly because with modern treatment, people with PD live much longer than ever before. In the past decade, physicians have developed a keener awareness of nonmotor symptoms of Parkinson's and their impact on quality of life for people with PD. These symptoms include personality changes such as the development of passivity, difficulty making decisions, loss of motivation, anxiety, depression and bradyphrenia (slowness in thinking). These and other nonmotor symptoms – including such problems as fatigue, sleep disturbances, constipation, bladder disturbances and changes in sensory perception – can become more serious when motor problems of PD are controlled with medications. Fortunately, many of these nonmotor symptoms can respond to treatment.

18. Effective medications that can reduce the severity of PD, however, are not always free of side-effects. Sometimes, serious adverse effects of hallucinations, delusions and paranoia can occur. The drug clozapine, not yet approved for PD, has been shown in clinical trials to ease such side-effects without aggravating Parkinsonian motor symptoms. In addition, in some people, PD medications known as dopamine agonists have been found to cause impulsive behaviors – most commonly pathologic gambling, compulsive eating and shopping – and hypersexuality. Reducing or stopping the medication eliminates these problems.

19. Researchers have learned that cognitive decline often occurs in people with PD when they reach an advanced age. This process has been traced to the presence of Lewy bodies in the brain's cerebral cortex, the area that is responsible for reasoning and decision-making. One medication, rivastigmine (Exelon®), is currently approved for and has been shown to be modestly effective for treating dementia in people with Parkinson's.

Advances in Treating PD

20. With therapies already in hand to control the symptoms of PD, the focus in recent years has been a search for medications that slow the rate at which PD progresses. Some drugs that looked promising based on testing in animals turned out not to be effective in humans. One class of drugs that may be effective in this regard is the MAO-B inhibitors. One of these is selegiline (Eldepryl®, Zelapar®); another is rasagiline (Azilect®).

21. Other agents, Coenzyme Q10 and creatine, are still in clinical trials. In other reassuring news, scientists found that levodopa – which was long suspected of worsening oxidative stress and possibly hastening the progression of PD – in fact may slow it down. The challenge of slowing down the progression of PD is also being addressed by scientists who are interested in exploring the neuroprotective value of physical exercise.

22. A number of controlled clinical trials have tested new therapies that control, but do not slow, symptoms. In general, researchers found a trade-off between the new treatments and levodopa, the gold standard: that is, the drugs that reduced motor fluctuations and dyskinesias (involuntary twisting and writhing movements) were less powerful than levodopa in alleviating Parkinsonian symptoms. One new medication, rotigotine (Neupro®), a dopamine agonist administered by a skin patch, came to market, but is currently unavailable in the US due to manufacturing problems.

23. Also, in the last decade, surgical deep brain stimulation (DBS) has been validated as an effective therapy for reducing dyskinesias and motor fluctuations in people who otherwise respond well to levodopa. However, many questions remain unanswered, including optimal timing of surgery and the long term outcome (more than five years after surgery) of the procedure. Other surgical approaches to therapy, including gene therapy, are now in clinical trials.

Gene therapy for Parkinson's disease

24. Parkinson's disease is characterized by loss of dopaminergic neurons in the substantia nigra. The loss of these neurons results in a change in the balance of excitatory and inhibitory pathways in the brain, and these pathways in turn affect movement control. Medication therapies, and in particular dopamine replacement therapies were developed in the late 1960s and remain the mainstay of therapy. More recently, surgical treatments (pallidotomy or deep brain stimulation of selected targets in the brain) have been developed to improve motor function by normalizing increased brain cell activity due the loss of dopamine releasing cells which occurs as a consequence of reduced dopamine release.

25. People with Parkinson's disease generally respond well to medication for a number of years. However with long-term treatment, the response to medication – especially to levodopa – may fluctuate. The most common "motor fluctuation" is called wearing off. Wearing off may develop years after beginning treatment with a dopamine agonist or levodopa. It occurs when the benefits of the prior dose are beginning to wane and is often appreciated as recurrence of tremor or slowness in the hour before the next dose of medication is taken. The other main motor fluctuation is involuntary twisting turning movements called dyskinesias which typically occur in the hour or so after taking dopaminergic therapies. Medications and deep brain stimulation are described in other modules. In this module, the potential advantages of gene therapy will be discussed.

26. Gene therapy has a number of potential advantages that may be useful in progressive medical conditions. Conceptually, it is a means of making cells produce a protein that normally do not produce that might improve a particular condition. The technique inserts genes that provide specific genetic instructions that cells use to produce a desired protein. The treatments produce proteins that are involved in normal cellular processes and may therefore be less likely to cause side effects. Moreover, gene therapy can be targeted to a specific location where the treatment is needed, which also may limit possible side effects. Finally, gene therapy does not rely on the placement of devices that may fail due to mechanical or electrical reasons. A number of proteins have already been used for gene therapy for Parkinson's disease. The choice depends on the treatment strategy.

Treatment Strategies

27. For example, one strategy is to improve the delivery of dopamine to the relevant brain regions in Parkinson's disease. Other strategies have tried to provide growth factor support to brain regions with the expectation that this might help damaged nerve cells to recover and thus slow Parkinson's disease progression or reverse it. Gene therapy relies on transporting small pieces of genetic material, or DNA, into the targeted brain cells. Because human bodies have developed a number of enzymes that breakdown unprotected DNA, most gene therapies use some sort of "protective envelop", called a vector, to carry the genetic material and deliver the gene to targeted cells. The most common vectors include adeno-associated virus type 2, lentivirus, adenovirus, and herpes simplex virus. Only viruses that have lost their ability to reproduce themselves and do not cause disease are selected as vectors for gene therapy. Adeno-associated virus type 2(AAV-2) has particular advantages. It carries genetic material only to neurons (not to the other supporting cells of the brain) and once within the brain it is particularly efficient in carrying the genetic material to the neurons affected in Parkinson's disease. Most gene therapy studies in Parkinson's disease have used AAV-2 as the vector. Lentiviruses have also been studied extensively. Because of their larger capacity, lentivirus is the vector when more than one gene is used. Once a gene and vector have been selected, the treatment must be administered to the relevant area of the brain. The studies performed thus far have been directed to particular regions of the basal ganglia. The basal ganglia are number of interconnected deep brain regions that are involved in movement control. A major pathway connects the substantia nigra to the putamen (where dopamine is normally released) and then to the globus pallidus directly or by way of the subthalamic nucleus.

28. To date, gene therapy for Parkinson's disease has been administered by drilling a hole in each side of the skull and then injecting the selected dose of the viral vector (containing the gene) into the desired brain region (either putamen or subthalamic nucleus) using image-guided surgical techniques. These treatments are performed either in a standard operating room or in a specialized radiology suite. Recovery from these procedures is usually quite rapid, with most patients being discharged home 1 or 2 days after gene therapy.

Conclusion

29. Limitations in the benefit of medical and the surgical treatments of Parkinson's disease have stimulated efforts to develop new therapies. Gene therapy has distinct advantages over conventional treatment for Parkinson's disease as it might preserve dopaminergic neurons through the use of growth factors or alternatively increase the availability of enzymes required for dopamine synthesis. Over the past 10 years, 3 different strategies have emerged and have been implemented in carefully designed human treatment protocols. To date, these gene therapies appear to be safe and there is some evidence suggesting benefit. Ongoing and planned phase 2 studies will identify the most promising therapies that will require further evaluation in a phase 3 study. It is hoped that gene therapies will provide improved treatment options for people with Parkinson's disease in the near future.

References and acknowledgements

Fahn, S (2009). Chasing the Cure: A Decade of Advances in Parkinson's Disease Research. *Parkinson's Disease Foundation News & Review*, Fall 2009. pp1–12

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