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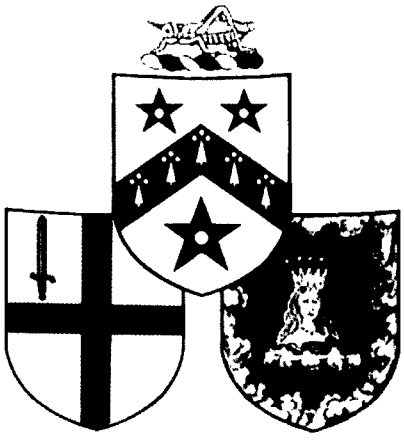

EXPLORING THE BRAIN

Lecture 13

PARKINSON'S DISEASE

by

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20 November 1997

GRESHAM COLLEGE

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Gresham Lecture Physic 13
Professor Susan Greenfield

Parkinson's Disease

In 1817 James Parkinson first reported the tragic triad of signs indicative of the brain disorder that now bears his name. This triad consists of: resting tremor a rhythmic shaking of the hands, and sometimes the feet, when at rest; dystonia, a rigidity of muscles that gives way in little jerks or 'cogwheels' when opposed in an arm wrestling scenario, and finally hypokinesia, a severe impairment in the generation of movement. This inability to move in no way reflects a lack of desire to move. Rather, it seems that it is the important link between thought and final contraction of muscle underlying movement, which is the problem with Parkinsonian patients. The difficulty is not so much at the level of the muscles, which are in fine working order, nor with a will to move, but rather the problem is at the interface between the two, between thought and action.

Parkinson's disease is caused by a drop in the transmitter dopamine in a key region deep down in the middle of the brain, the 'substantia nigra': the substantia nigra is so called because of the black pigment melanin contained within the dopamine cells. It has been known for a long time that there is a frank loss of these neurons primarily in this highly localised region, where the dopamine cells are distributed as a thin arching sheet on either side of the brain. At least seventy percent of dopamine neurons in the substantia nigra must be lost before any deficit in movement is seen: unremittingly, the whole population slowly degenerates, so that what was once a relatively small cell loss ends up as virtual extinction of a complete brain region. This is a prime example of 'necrotic' death: neurodegeneration.

Assume, for the time being, that the process of degeneration has been initiated. This subsequent degenerative process is slow, over a time scale of years. One idea is that as a few cells die, then neighbouring neurons attempt to compensate for the loss, in a way comparable with the compensation that clearly occurs in the motor cortex: indeed we know that this scenario is likely since up the majority of cells must be lost before the behavioural problems of Parkinson's disease are apparent. In the substantia nigra, the compensation for loss of dopaminergic neurons, would be to increase the amount of dopamine

released from the still surviving cells. A possible explanation of how the cells in the substantia nigra could be gradually killed in this way stems from the normal metabolism of dopamine.

It is necessary for all transmitter substances to be removed in some way from the site of action at their target receptor, and dopamine is no exception. However, unlike other transmitter substances, the removal of dopamine by conversion to a more inert metabolite product, is potentially rather dangerous. Both within the nerve terminal and at the corresponding target site, the metabolism of dopamine yields a by-product, hydrogen peroxide, (H_2O_2):

dopamine + H_2O-----> 3,4-dihydroxyphenylacetaldehyde + H_2O_2 + NH_3

This hydrogen peroxide rapidly dissociates, by means of the Fenton Reaction, to yield the toxic hydroxyl (.OH) free radicals, which is lethal to the neuron, in that it causes disintegration of the membrane. However, the chain of events is not quite so simple as it might first appear. In order for the killer free radical to be generated from hydrogen peroxide, we have already seen that iron (Fe) must be present to act as a catalyst.

On the other hand, a misfortune might be able to be turned into a novel therapy. If the final cause of Parkinsonian cell death is indeed the presence of iron, why not give substances which bind the iron to them (chelators), so that the metal becomes inactive? This idea is currently being explored clinically. However, there is a potential problem. The enzyme, tyrosine hydroxylase, that makes the all important dopamine, itself requires iron to function. Paradoxically therefore, there are some who actually recommend quite the opposite treatment for Parkinson's disease: instead of inactivating the iron, it might be beneficial to supply even more. Iron administration as the iron compound oxyferriscorbone can increase tyrosine hydoxylase activity some twenty fold: is even possible that iron activates the dopamine receptor. On the other hand, the long latency of this effect of iron on receptors exceeds the time frame for the therapeutic effect of iron in Parkinson's disease.

This paradox, whether iron is a beneficial or pernicious factor, illustrates the problem of understanding the mechanisms of the necrotic death in degenerative disorders in the brain. If one factor is changed it can upset the balance between a whole series of reactions. There is no simple causal chain, but rather all factors are interdependent. It is nonetheless undisputed that the

generation of free radicals occurs. In the substantia nigra of parkinsonian patients post mortem there is a significantly higher level of free radical activity than in the intact substantia nigra of those without Parkinson's disease, but of a similar age. The next question is then: why is not dopamine always leading to generation of free radicals? What prevents this inevitable process, of generating a toxic agent by normal transmitter metabolism, from always killing substantia nigra cells and giving everyone Parkinson's disease?

The answer is that normally in the brain, dopamine does generate free radicals, but normally in the brain there are defence mechanisms. Here is a list of the 'scavenger' mechanisms available to combat and neutralise the free radicals. In older people levels of some scavengers, such as glutathione, decline and it could well be more than coincidental that Parkinson's disease is characterized most commonly by onset after sixty years of age. In addition, the activity of the enzyme that oxidises dopamine (MAO), increases with age, and molecule for molecule yields an increase in production of H_2O_2. It is only when there is an abnormal production of hydrogen peroxide, that neuronal damage might be caused. A high production of this by-product would result from an exuberant synthesis of dopamine, which in turn would only occur in an attempt to counteract a deficiency of the transmitter. Imagine therefore a small initial cell loss which, for whatever reason, triggers off a compensation that mis-fires, namely a high production of dopamine that itself generates toxic free radicals. It has been shown that pharmacological treatments that enhance dopamine turnover, do indeed cause an increase in oxidised glutathione, which in turn indicate an increase in the generation of free radicals. In this way, the degeneration process would be set in train.

The availability of dopamine can also be increased by yet another means: lack of local oxygen, hypoxia. If there is a minor stroke in the vicinity of the substantia nigra, the lack of oxygen will lead to a depletion of energy because ATP can no longer be synthesised. If the cell has no energy, then normal processes such as the uptake of dopamine back into the cell will cease, and dopamine will remain at large. Instead of being recycled within the cell, this excess dopamine will then be broken down so that the process yields even more free radicals. However there is a drug that can start to counteract this problem: this drug works by preventing the destruction of dopamine, by blocking the relevant enzyme MAO. This strategy would have obvious benefits for two reasons: the valuable dopamine would be conserved to fulfil its normal role in the control of movement, and in addition, production of the toxic free radicals

would be reduced. This MAO inhibitor, (Deprenyl), is now given as an adjunct to complement to the now well established therapy of administration of the dopamine precursor L-DOPA.

In the 1950s the neurochemist Marthe Vogt made a discovery that was to revolutionise the understanding of the brain in both health and disease. She showed that amines such as noradrenaline and its precusor dopamine were not, as had been thought , merely associated with blood vessels in the brain, but were actually intrinsic to brain tissue as working transmitters in CNS neurons. A subsequent major break through was made by Hornykiewicz who measured levels of dopamine in the brains of Parkinsonian patients, and found that there was a dramatic reduction, compared to normal brains, in the substantia nigra and its target region the striatum: the nigrostriatal system. This discovery prompted the development of an entirely new therapy for Parkinson's disease, based on the idea of replenishing the dopamine that is lost when the dopaminergic neurons die. However, because dopamine carries a charge, it is not lipid soluble and cannot thus pass readily into the brain via the blood-brain barrier. On the other hand, its pre-cursor, L-DOPA can cross the blood-brain barrier. When L-DOPA was given to patients initially, it was indeed found to have a remarkable therapeutic action within only thirty minutes or so, but only at high doses. The problem was that the L-DOPA was being converted into dopamine by the body, before it had chance to gain access to the brain. The strategy for circumventing this problem is now to prevent the conversion of L-DOPA to dopamine by inhibiting the enzyme responsible, DOPA decarboxlase. The decarboxlase inhibitor (carbidopa) is designed to work only outside the brain, as its structure will not let it pass the blood-brain barrier. Hence now only small doses of L-DOPA need be given, which will be protected whilst outside of the brain, but which will be converted into the much needed dopamine inside the brain. It is more effective than direct stimulation of dopamine receptors with drugs such as bromocriptine, since the prolonged activation of receptors independent of the process of normal neuronal transmission, causes them to become less sensitive and the drug thus eventually less effective. L-DOPA/carbidopa, which works on the transmitter dopamine itself, thus operates in a more 'natural' physiological way and is thus still the drug treatment of choice in Parkinson's disease. However, this treatment does not slow down the progress of neurodegeneration, only combats its symptoms. In addition, L-DOPA will also increase dopamine levels in brain regions not effected in Parkinson's disease. Hence, side effects such as hallucinations can occur.

It seems then that a calcium ion can also be both a good friend and deadly enemy, a neuronal Jekyll and Hyde, depending on its quantity. In early stages of development, neurons can withstand and indeed flourish on three times the amount of calcium that would prove toxic to neurons in the mature system.

It could be the case, therefore, that both the developing and mature nervous system has in one mechanism, namely calcium entry, a means to change, and also a means to destroy. Since this destruction however, is caused by entry of calcium ions, the process will always be preceded by a brief period of depolarization identifiable as excitation. This biphasic action has given rise to the term 'excitotoxicity'.

Clearly then, modification to calcium entry might prove an alternative treatment for Parkinson's disease in the future, which would be especially valuable if the patient was developing tolerance to L-DOPA. The chief problem, however, is to identify Parkinsonian patients early on in their disease. Due to compensation mechanisms in the substantia nigra, no signs of movement disorder are apparent until almost three quarters of the dopaminergic nigral cells are already destroyed.

Nonetheless, an understanding of Parkinson's disease will not hinge around dopamine alone, but rather on how dopamine interacts with other transmitter systems, such as glutamate. At first glance such a complex interplay of transmitters might augur poorly for the final development of a more successful drug therapy than L-DOPA, which does not actually arrest the degeneration of cells in the substantia nigra. After all, if there is no single chemical at fault, that can be manipulated independent of all others, what chance of any new treatment?

Another, more optimistic way of interpreting the situation would be to actually exploit all the complex interactions. The more we know of the chemical signature that makes up, in this case, the substantia nigra the more accurate we might be in designing a drug 'cocktail'. Such a cocktail would consist of drugs in an insufficient amount to affect any other brain regions on their own (thus reducing the problems of side effects), but in combination could restore the balance of power between certain transmitters in a circuit, such as that in the substantia nigra. The more detailed our knowledge of the normal

chemical interactions, the normal 'balance of power', the more specific would be the cocktail for exploiting these interactions in the substantia nigra specifically, and thus targeting only the malfunctioning brain area. Hence the more we know of the concerts of chemicals at work in each brain region, the greater our chance for progressing to understanding the development and treatment of currently incurable disorders.

In general, the substantia nigra serves as a good example of the many and diverse chemical balancing acts that are in use to maintain neuronal homeostasis in the brain. The important principle to keep in mind is that no substance involved in the process of degeneration need be intrinsically toxic. Even free radicals can be scavenged, or eliminated by reaction with other free radicals, such as the far more stable nitric oxide and naturally occurring antioxidants. Secondly, an excess of virtually anything in the brain is a potentially toxic instrument: calcium ions, dopamine, glutamate and even the scavenger glutathione, since it is metabolically linked to the excitatory agent, glutamate, which we have seen, in excess can act as an excitotoxin. Thirdly, it would be wrong to simply concentrate on the neurons themselves, since the glial cells play an important role in maintaining a beneficial milieu and indeed of providing a source for the enzyme which would break down dopamine. Finally, no transmitter system works in isolation, but depends for its effects on an interplay with other systems, which in turn feeds back to modify each transmitter system further.

If then, as seems to be the case, there is no villainous substance, but rather a disorder of chemical interaction, many of the frustrating features of the degenerative CNS disorders would be understood: the elusive nature of a single 'cause', the slow onset due to compensatory mechanisms, the gradual loss of cells, the failure to find an effective treatment without side effects. On the other hand, such a rich tapestry of chemical interactions should ultimately offer the hope of a wide variety of pharmaceutical strategies.