Agricultural toxins and the risk of Parkinson’s disease – could genetics be the key?

Recent research shows that chronic exposure to paraquat – which is no longer used in the European Union – could even be linked to a higher risk of Parkinson’s disease. Byrom Jones, Professor of Genetics at the University of Tennessee, is studying how this herbicide could destroy brain cells and how genes decide who is more at risk to its neurotoxic effects.

Paraquat is a widely used weedkiller with fast and effective results for ridding farms and gardens of unwanted green plants. However, as with most pesticides, it can have toxic effects. Recent research shows that chronic exposure to paraquat – which is no longer used in the European Union – could even be linked to a higher risk of Parkinson’s disease (PD). A number of observational studies have indicated that agricultural workers are more likely to develop PD than people in the general population, and further investigations suggest that this risk is due to exposure to toxic herbicides. Further, a recent brain scan project has shown that agricultural workers who have had chronic exposure have differences in their brain microstructure compared with controls.

Parkinson’s disease (PD) is an incurable neurodegenerative disease characterised by a lack of motor coordination and progressive cognitive decline. Pathological changes underlying PD can be detected throughout the brain in patients, although the key region is the substantia nigra in the midbrain, where brain cells involved in transporting the neurotransmitter dopamine are lost. Loss of these dopaminergic neurons leads to a lack of motor control, which slows movement and causes rigidity and the distinctive tremor associated with the disease.

PD falls into two categories, familial or sporadic. Familial PD affects a minority of cases and has high levels of heritability with a number of genes identified as having a potentially causative effect. In contrast, sporadic cases are more common, but the aetiology is less clear-cut and likely to be complex, involving a number of genes. As with other sporadic cases of neurodegenerative diseases, including Alzheimer’s disease, environmental and lifestyle factors inevitably play a role. Increasing evidence suggests that rural life is associated with a higher risk for developing sporadic PD, with chemicals used in agriculture becoming the prime suspect.

Susceptibility
Inconsistencies in the literature in both public health and animal model studies suggest that the link between paraquat and PD is not clear-cut. However, Prof Byrom Jones suspects that some of these inconsistencies are due, not to a lack of a relationship, but to heterogeneity in people and animals tested, clouding the interpretation of the data, which fails to take individual differences into account. His hypothesis is that some people exposed to paraquat could be more susceptible than others to the risk of PD, despite living and working in the same environment.

To address this, Prof Jones and his team are turning to genetics to identify the risk factors that might modify susceptibility and the mechanism of neurotoxicity using genetically well-defined mouse models.

In a recent study, following injections of paraquat, two strains of mice showed different...
numbers of dopaminergic neurons affected by the toxin, despite having equivalent amounts of it in the midbrain. These findings highlight the importance of genetics on susceptibility to paraquat’s effects and will enable scientists to ‘reverse’ investigate what genes and biochemical pathways could be moderating this. Determining a ‘toxicant-sensitive genotype’ will be key to identifying humans who might be at increased risk of PD due to paraquat exposure and could therefore be vital to the safety of agricultural workers.

Prof Jones has launched a five-year study investigating susceptibility and the mechanism of neurotoxicity using genetically well-defined mouse models

MECHANISMS
Potential mechanisms through which the herbicide could cause PD have not been fully elucidated. Current thinking suggests that paraquat is linked to an increase in the production of damaging reactive oxygen species or free radicals. The damaging effects of these oxidative species lead to dysfunction and death of dopamine neurons that are linked to the onset of PD.

A key modulator may be the regulation of iron in the substantia nigra. Paraquat may alter the regulation of iron in the substantia nigra.

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What first made you want to study agricultural neurotoxicity?
While I was at Penn State, I became aware of some of the neurological problems posed by the use of pesticides and because I have a long-standing interest in dopamine, paraquat became the first candidate toxicant to study.

Do you think the data are strong enough yet to warrant a widespread ban on paraquat?
The evidence seems to be sufficient that Northern European countries and Ecuador have banned its use.

Do genes also influence susceptibility to more commonly used toxins, for example, alcohol?
There is good evidence in support of this idea.

Do familial and sporadic PD have different symptoms?
I am not a neurologist, but my reading of the disease is no.

Could it be possible to develop a protective drug that could reduce harm for farmers using paraquat?
Perhaps. Drugs that increase dopamine function would be one candidate – maybe Ritalin?

Where do you see your research leading in the future?
I see a need to understand better the pathology of Parkinson’s disease. It is essential if we are to develop improved treatments.

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