Environmental explanations

Drs Peter Spencer and Glen Kisby explain how their collaborative research is shedding new light on the environmental origins of neurodegenerative diseases and the relationship these diseases have with cancer.

Having worked together on neurodegenerative diseases for many years, can you begin by outlining the circumstances that led to your current research focus and how you began this collaboration?

PS: In the 1970s at the Albert Einstein College of Medicine, New York, USA, I began a systematic analysis of how chemicals of synthetic or natural origin attack different cellular components of the nervous system and cause neurological diseases. The analysis, backed by experimentation, proceeded well until I reached the motor neuron in the spinal cord, where I was unable to identify chemicals that specifically attacked motor neurons. A prolonged library search revealed two little-known motor neuron diseases, one of which was caused by eating a toxic legume – lathyrism – and the other also of probable environmental origin – amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC).

GK: I joined the Spencer laboratory as a postdoctoral researcher in 1986, where I studied these diseases in partnership with Dr Spencer and other colleagues. Our papers in 1988 and 1992 described analytical methods to quantify the plant excitotoxins and genotoxins linked to these motor system diseases. Thereafter, we worked together on both diseases, with Spencer focusing on plant amino acids (BOAA/BMAA) – linked to lathyrism and ALS-PDC – while I concentrated on a plant toxin, cycasin, and its metabolite, methylazoxymethanol (MAM) – linked to ALS-PDC.

What are your individual backgrounds and what expertise do you both bring to this project?

PS: My training was in the neurological sciences and pathology, and my career has focused on developing a science of neurotoxicology.

GK: I trained as a pharmacist and pharmacologist/toxicologist. Prior to joining the Spencer lab in the late 1980s, I investigated the long-term effects of environmental chemicals, such as metals, on nerve function.

You have highlighted the importance of preventing these neurodegenerative diseases as opposed to treating them; has your research initiated any programmes to facilitate prevention in the areas you have worked?

PS&GK: The lathyrism research with Valerie Palmer (picture on p53) stimulated a pre-internet, worldwide multidisciplinary scientific cooperation, organised by the Third World Medical Research Foundation, that aimed to develop safe, low-toxin strains of the grasspea – a legume with many positive features including high protein content, nitrogen fixation, luxuriant growth, pest resistance, extreme environmental tolerance and low cost.

The ALS-PDC research resulted in a ban on the sale and use of cycad seed for medicinal purposes in Japan and an awareness of the hazards associated with use of cycad seed for food and medicine.

What problems do researchers face when working with isolated communities, particularly in terms of funding?

PS&GK: National funding is usually focused on nationally prominent diseases, which places disorders like lathyrism and western Pacific ALS-PDC very low on the totem pole. We also encounter resistance to the provision of funds for foreign travel, and the belief that disease isolates are peculiar accidents of nature and therefore unworthy of much effort to understand.

In addition, there is an unfortunate blind-spot in the environmental sciences, with little interest in plant chemicals other than those derived from tobacco or those used to induce euphoria in the form of illicit drugs.

How can work on diseases with clear causal factors aid research into neurodegenerative diseases that have proved more difficult to unravel, such as Alzheimer’s disease? Are there any neurotoxins that have already been implicated in Alzheimer’s?

PS&GK: Cigarette smoking has been linked to an increased risk of Alzheimer’s disease but imaginative epidemiological studies that search for other possible exposures are lacking, in part because there is a very long latent period between exposure to culpable agents and clinical appearance of disease symptoms. There is also a paucity of research that examines the relationships between various forms of neurodegenerative disease. Chinese researchers have published evidence linking Alzheimer’s disease with increased formaldehyde in the body, but these data have yet to be confirmed by other investigators. We have noted the chemical similarities between the cycad neurotoxin methylazoxymethanol (MAM) and nitrosamines found in food and industry, the latter having been independently linked to Alzheimer’s disease by another research group. The amino acid BMAA has recently sparked enormous interest in relation to ALS because it has been found to be generated worldwide by cyanobacteria in soil and water that contaminate filter feeders used for human food. Further research certainly needs to be conducted in these areas.

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Brain degeneration, cancer connections

Researchers based at Oregon Health & Science University and Western University of Health Sciences are collaborating to investigate the links between neurodegenerative diseases and their relationship to cancer.

AGEING POPULATIONS

are impacting societies across the world, giving rise to an increasing incidence of age-related neurodegenerative disorders. This is a particular concern for policy makers and health officials in many high income countries. For example, in the UK alone, current projections estimate a doubling of the number of people aged 65 or over, reaching approximately 19 million by 2050. Given the prevalence of certain neurodegenerative disorders, it is alarming to discover that relatively little is known about their aetiology. In view of the growing health, social and economic burdens these diseases are likely to place on societies worldwide, there is an urgent need for innovative studies that scrutinise their aetiology and pathogenesis in detail.

Two prominent researchers responding to this need are Drs Peter Spencer and Glen Kisby. Spencer is based in Neurology and the Global Health Center at Oregon Health & Science University, USA, while Kisby is located at the College of Osteopathic Medicine in the Western University of Health Sciences, USA. The two scientists have collaborated for nearly three decades, studying the potential environmental origins of neurodegenerative disorders and primarily focusing on exploring a prototypical neurodegenerative disease found exclusively in the Western Pacific region. Understanding the mechanisms that underpin this disease could generate an enhanced understanding of analogous disorders throughout the world.

DEADLY DISEASE

Spencer and Kisby are researching western Pacific amyotrophic lateral sclerosis and parkinsonism-dementia complex (ALS-PDC), a progressive, fatal brain disorder that may present at onset as motor neuron disease, parkinsonism, pre-senile dementia or various combinations of all three. In the same way that the Rosetta Stone bears the inscription of three different translations of the same message, these three clinical forms of ALS-PDC share a common pathology, resulting in the eponym the ‘Rosetta Stone of neurodegenerative diseases’. Formerly found in very high incidence in three genetically disparate populations in the Western Pacific – Chamorro people of Guam, Japanese residents of Honshu Island’s southern Kii peninsula and Indonesians in West Papua – this non-transmissible disease has since declined rapidly as affected communities have modernised. The declining incidence of this disease in all three populations implicates an environmental factor, likely common to all three populations, that is disappearing with modernity; this factor must be of natural origin because ALS-PDC was present in New Guinea prior to the introduction of man-made materials.

Starting in the 1980s, Spencer and his colleagues researched the environmental causes of another motor neuron disease in Bangladesh, China, India, Ethiopia and Spain. The disease in question is lathyrism, which had an established environmental aetiology stemming from prolonged dietary dependence on the grasspea (Lathyrus sativus) and other neurotoxic Lathyrus species.

ENVIRONMENTAL ORIGIN

Spencer’s initial field and epidemiological studies on lathyrism led to the development of a primate model for the disorder. His team fed macaques the grasspea or its key neurotoxin, the amino acid BOAA, which excites and kills neurons. Studies with mouse brain and spinal cord tissue demonstrated that BOAA selectively acted at the nerve cell AMPA receptor, which modulates...
Fast excitatory neurotransmission. Parallel research with a related amino acid isolated from cycads, the neurotoxic seed of which was used by Chamorros for food and medicine, provided a crucial possible link with western Pacific ALS-PDC. Named BMAA by Spencer, the cycad amino acid was also shown to have excitotoxic properties and induce a primate motor system disorder distinct from BOAA. Building on this, Spencer and his team then demonstrated in field studies that individuals with ALS-PDC in Guam, Kii-Japan, and West Papua had commonly used raw cycad seed for medicine.

THE CANCER LINK

More recently, Spencer and Kisby have identified a relationship between the neurodegenerative and carcinogenic properties of cycads. This stemmed from their research in Guam, where they demonstrated a strong correlation between ALS-PDC and the concentration of cycasin – the main cycad genotoxin – in the Chamorro flour used to make tortillas. Crucially, not only has the active component of cycasin – methylazoxymethanol (MAM) – been used as a tool to induce brain maldevelopment in laboratory rodents since the 1970s, but it is also a well-established carcinogen that produces an animal model of colon cancer. To determine how exposure to a genotoxin could also induce a neurological disorder, Spencer and Kisby used a DNA repair-deficient mouse model to compare the different cellular pathways disrupted by MAM. Their gene and protein expression studies found evidence of molecular mechanistic links between cancer and neurodegeneration.

Specifically, the researchers found that MAM activates pathways in brain cells that are linked to neurodegenerative disorders, as well as pathways in colon cells that result in tumours. Thus the impact of MAM appears to depend on the cell type it targets; in gut cells, it causes uncontrolled cell division while in nerve cells it causes degeneration. These initial observations have contributed to a growing body of evidence that suggests there is a mechanistic connection between cancer and Alzheimer’s disease.

FUTURE PLANS

Spencer and Kisby’s collaborative research testifies to the importance of field studies on rare diseases, the necessity of understanding the environmental settings in which these diseases occur, and the beneficial impact of involving the afflicted populations in data gathering and information sharing. While they have yet to collect conclusive evidence that exposure to cycads causes ALS-PDC, it is easily the most plausible agent to date. Furthermore, their investigations have uncovered the key role of environmental factors in the pathogenesis of neurodegenerative disorders, close aetiologic connections between different brain disorders and strong associations between ageing, neurodegeneration and cancer.

Looking ahead, Spencer and Kisby are planning to continue exploring the connection between brain degeneration and cancer. One specific experimental focus will be on the role of formaldehyde, a carcinogen and metabolite of MAM and BMAA, which has also been linked to Alzheimer’s disease. Ultimately, the hope is that their ambitious research projects will forge new insights into the aetiology of lookalike neurodegenerative disorders throughout the world, eventually leading to the discovery of robust prevention and therapeutic strategies.