THE SEARCH FOR PLANTS TO MANAGE NEURODEGENERATIVE DISEASES

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Keywords: Alzheimer's disease, Parkinson's disease, alkaloids, acetylcholinesterase inhibitors, huperzine A, galanthamine, L-DOPA, physostigmine, rivastigmine, ginkgo.

Contents

Summary

The major neurodegenerative diseases are Alzheimer's disease (AD) and Parkinson's disease (PD), associated with deficiencies in the central nervous system of the neurotransmitters acetylcholine and dopamine respectively. Factors are considered which appear to increase or decrease the risk of contracting these diseases since plants

which inhibit or enhance such effects respectively may be useful in prevention of these diseases.

Plants from Indian, Chinese, European and South American traditional medicine systems have been investigated and found to yield compounds and extracts which give symptomatic relief and help control both of these diseases. In some cases the plants have been used for conditions very similar to AD or PD but in other cases they have been used for other ailments, and their value in treating neurodegenerative effects has been found as a by-product of other investigations. The knowledge of the mode of action of the active constituents of plants used as poisons has been applied in treating the condition. Plants of use include those which are the source of single compounds and those where a variety of compounds and activities all contribute to an overall effect.

Individual compounds are mainly used to increase the levels of deficient compounds, either by acting on the same receptors or by inhibiting enzymes which cause a drop in levels of the transmitters by metabolising them. Acetylcholinesterase inhibitors which have been exploited in this way are huperzine A from the ancient Chinese remedy based on *Huperzia serrata* and galanthamine from *Narcissus* and *Galanthus* species. Another group of acetylcholinesterase inhibitors has been derived from physostigmine, the active component of the ordeal poison from the Calabar bean. Compounds which increase levels of dopamine in PD include L-DOPA from various beans and derivatives of the ergot alkaloids. Plant extracts with a variety of activities and compounds include Gingko and some species of *Salvia*.

1. Introduction

1.1 Neurodegenerative disease in perspective

Neurodegenerative disease is a generic term applied to a variety of conditions arising from a chronic breakdown and deterioration of the nerve cells, particularly those of the Central Nervous System (CNS). In addition the neurones accumulate fibrillary materials which cause dysfunction. Alzheimer's disease (AD) and Parkinson's Disease or Parkinsonism (PD) are the two best-known diseases of this type but many psychiatrists and neurophysiologists recognise several other similar diseases as well as those with a much lower incidence. The spongiform encephalopathies could also be categorised as neurodegenerative diseases and have received much publicity in recent years due to the apparent link between eating infected beef and of development of Creutzfelt-Jacob disease (CJD) in humans. The incidence of CJD is very low at present but a similar disease in sheep, scrapie, is of much greater economic importance. These diseases have been shown to be caused by prions, proteinaceous particles synthesised within the cell which replicate and accumulate in cells and so alter protein structure and therefore function.

Most commonly, neurodegenerative disease manifests in elderly people and, in advanced industrialised and post-industrialised societies, where life expectancy is long, this group of conditions is a major cause of morbidity and of death, as well as imposing severe strains on the social welfare systems e.g. in the USA, AD now affects at least 5 million people and in the UK in 2001 it affected 750 000 people and was the fourth

most common cause of death. The financial costs are very large, e.g. in the USA estimated health costs alone in 1998 amounted to US$100 billion. Although at present the greatest focus is on the developed world, it is important to note that the WHO estimates that 70% of the population aged 65 years or older will be living in the developing countries by 2020 and the consequent increase in the number of neurodegenerative disease cases there will be yet another burden on the already hard-pressed financial and labour reserves of such countries.

Although the common symptoms of neurodegenerative diseases, such as loss of memory and tremor, are recognised as a feature of increasing age in many medical systems, it is only comparatively recently that distinctive diseases have been identified and received much attention from mainstream medicine. This is most likely due to the fact that a short life expectancy precluded many surviving to an age where neurodegeneration was likely to affect a significant part of the population, although it has been argued that some of the factors apparently linked with an incidence of neurodegeneration, e.g. AD, were not so prevalent in previous generations and so the incidence would have been much lower.

The same arguments could be used to explain the low profile often given to diseases of this type in many traditional medicine systems. In addition, it is possible that the negative symptoms of ageing were taken for granted and older people were not considered a burden to society but were accepted and cared for in the extended family. It should be noted, however, that, in many societies, the much greater respect afforded to the views and decisions of the elderly suggests that maintenance of an active mind in old age was considered desirable.

Where collected ethnopharmacological writings exist, a preventive aspect is often mentioned as well as a curative one and this is often related to diet as much as more specifically medical treatment. It is interesting to note that the links between diet and health have become much more accepted in Western medicine over the last two decades, particularly in an attempt to prevent the development of even higher rates of incidence of fatal cardiovascular diseases, such as heart attack and stroke. In many traditional societies, the widespread use of preventative practices, including plants added to the diet, would be another factor to explain the apparently low incidence of neurodegenerative diseases.

A preventative approach necessitates consideration of which factors predispose individuals to, or protect them from, neurodegenerative diseases. This evidence is obtained by various means such as genetic and epidemiological studies but clear links are very difficult to establish. For the commoner diseases, an association between the disease and a deficiency or imbalance in the chemicals involved in neurotransmission has been established, but the underlying causes or triggers for the deficiency are only beginning to be investigated. Thus, AD is linked with low levels of acetylcholine in some areas of the brain and PD with reduced levels of dopamine in the *striatum nigrum* but the causes of these low levels are not definitively known. Other histological features are seen in brain tissue examined post mortem and the presence of neurofibrillary tangles and plaques of a protein named β-amyloid are characteristic of AD patients. The degeneration of neurones, in common with other physical symptoms associated with the

ageing process, is thought to implicate oxygen free radical attack on the unsaturated lipids found in the cell membranes. Although the formation of oxygen free radicals is an important part of the body's defence system, an excess may be produced, due to inflammation, diet, excess of some metal ions, infection and several other factors, so unbalancing the natural equilibrium and generating excessive damage.

Defective calcium homeostasis and mitochondrial dysfunction are also thought to be implicated in both apoptotic and necrotic death of the nerve cells in AD. In PD there is an inclusion in the neurones of a deposit called Lewy bodies and oxidative stress from an excess of oxygen free radicals is again thought to be important in the development of PD in an individual.

Research into the underlying chemistry and biochemistry is far from complete and no cures for these diseases have been introduced in Western medicine. The current therapeutic approach is to produce symptomatic relief in the early stages of these diseases by correcting the deficiencies in the neurotransmitters by agonists or by inhibiting the enzymatic breakdown of the transmitters, although recently inhibitors of the enzyme involved in forming the β-amyloid plaques have been investigated. An N-methyl-D-aspartate (NMDA) receptor antagonist drug, memantine, that affects glutamate transmission, is also in clinical use for moderate to severe Alzheimer's disease. Some of the therapeutic agents used today have been developed from traditional medicines and are discussed below but it should also be noted that screening traditional medicines for the same activities as those exploited therapeutically, has revealed that some of them, at least, display activities that could explain their reputed effectiveness.

1.2. Searching for symptoms in traditional medicine

In common with many other disease states recognised by modern orthodox 'Western' medicine, neurodegenerative diseases were not known as such in previous generations or are described differently in other cultures. It is therefore highly unlikely that discussions with traditional healers or recourse to historical literature will yield much information if modern medical terms are used and so an approach whereby information according to the treatment of characteristic symptoms is sought is probably more profitable.

It is therefore apposite to know the main symptoms of the major neurodegenerative diseases, AD and PD.

AD is characterised by loss of short-term, and eventually long-term, memory as a feature of general cognitive decline. In the later stages of the disease language deficits, depression and agitation are common. Investigations into traditional uses should therefore be focussed on substances which improve memory, cause a general stimulation of thought processes and relieve depression, in whichever way it is viewed in a particular cultural context.

PD is known because of the characteristic tremor that is associated with it, although difficulty in movement and stiffness are other frequently-encountered symptoms,

particularly a shuffling gait. These are easily recognised characteristics which can be used in searching for possible agents for alleviation of the disease.

As well as those materials used medicinally, clues to possible usefulness may be obtained from poisons that act by producing levels of compounds in the body that are considerably higher than normal. These compounds may counteract in some way the aspects of the disease. This is particularly true of toxins which either mimic the action of the deficient neurotransmitters or which reduce the rate at which they are broken down in the body. Compounds which are converted to dopamine or which have a dopaminergic effect on the dopamine receptors would be rated as toxic since they are likely to produce nausea, vomiting and a high pulse rate at high doses. If such symptoms are noted when poisoning occurs it would indicate that the plant from which the poison was derived would be of interest in treating PD since it is likely to elevate dopamine levels. In a similar way, compounds which inhibit the breakdown of acetylcholine by inhibition of acetylcholinesterase would be of potential use in AD and would give symptoms of cholinergic stimulation, such as sweating, flushing of skin and painful contractions of the intestinal tract.

It should be noted that the understanding of the causes of a disease in Western medicine is not always the same as that in other traditions. The understood causes are related to the observed symptoms and will influence the approach to treatment. Many African cultures include spiritual factors in the cause of disease whilst Ayurvedic and Chinese medicine view the correction of imbalance as the key to treatment. The interpretation of medical conditions described according to these viewpoints to orthodox medical thinking often poses problems and some knowledge of the relationship between described and observed symptoms may be necessary.

1.3. Approaches to scientific investigation

Once an agent of interest has been identified from medical or toxicological observations or data, there are a variety of ways in which any scientific evidence for its presumed effects can be produced.

The most satisfactory way of demonstrating efficacy of a material, from a point of view solely concerned with the strength of evidence, is to undertake a well-designed clinical trial. This will have considered a variety of important points including the number of participants, the selection criteria for the participants, the use of placebos and/or a positive control, which is a known effective treatment, the outcomes to be measured, double-blinding and randomisation, the statistical analysis of the data and ethical aspects. However, this approach is hardly ever used in preliminary investigations, unless the material is already used or ingested widely without apparent adverse effects. As well as safety aspects, other factors which militate against clinical trials are the high costs involved and the need to recruit clinicians with interest in the product. In general it is also not common for trials to be conducted for minor illnesses. Neurodegenerative diseases do not fall into this latter category but, because of the unknown chemical constitution, and therefore pharmacology and toxicology of a traditional remedy, few studies have been performed until a single chemical entity, an 'active ingredient' has been isolated and preliminary studies in animals have been carried out. Healthy

volunteers can be used to investigate cognitive performance and a statistically significant improvement in subjects treated with a compound or extract compared with control might be translatable into therapeutic usefulness in patients suffering from loss of cognitive function. This approach has been used in recent studies on sage (see below).

Clinical trials for medicinal agents are usually preceded by studies in living animals which act as models for the human disease. Although relatively small and fast-breeding animals, such as rats and mice, can be used to display many diseases known in humans, this does not apply to some neurodegenerative diseases, and other animal models may have to be used which may be expensive e.g. primates are used for the study of PD. Tests for behaviour related to cognitive function using animals have been carried out in some instances as indicators of substances which might be of value in neurodegenerative conditions where cognition is affected.

In the absence of whole animal models, tissue studies may be undertaken. Brain tissue is expensive and relatively difficult to obtain and maintain. Slices of the appropriate region are taken and have to be kept alive in a suitable medium. Such preparations may be useful for staining to observe certain structures and chemicals so that the effect of test materials added to the tissue can be observed and measured. In the same way, the release of neurotransmitters in the absence or presence of the material under test can be assessed by measuring their concentration in the superfusion fluid. The rate of release of dopamine from striatal cells has been used in this way to investigate the effects of *Banisteriopsis caapi* which might be relevant to its claims as an anti-PD substance. Receptor-binding studies can also be performed using tissue slices or cultured cells and, since at one stage estrogenic compounds were thought to confer some protection against development of AD, the ability of substances to bind to estrogen receptors has been assessed using cell-based assays.

If particular cell types of interest can be isolated and grown in culture, they can be used for studies, especially of agents that might cause proliferation of neuronal cells. The relevance of this to neurodegenerative disease, is that such proliferation in the CNS might replace nerve cells lost because of the disease and so give a measure of restoration of mental function. Although some extracts and compounds have shown such activity, it still appears some time before the plants and compounds responsible are used therapeutically.

The final approach encompasses methods which have been used fairly extensively in recent years in the screening of plants and other materials. It is based on the inhibition of enzymes relevant to the levels of neurotransmitters and other substance in the CNS. These enzymatic methods require only small amounts of material and yield results which can be quantified easily, so they are very useful in bioassay-guided fractionation to isolate active components of extracts. Investigations to determine compounds which might be of use in PD in elevating dopamine levels are based on inhibition of monamine oxidases (MAOs) whilst a similar approach for AD is to seek inhibitors of acetylcholinesterase (AChE). Both approaches are based on spectrophotometric determinations and in situ detection of compounds on TLC plates.

Tests of this type are also used to determine antioxidant activity, which is relevant to neurodegenerative disease, since reactive oxygen species are thought to be implicated in neuronal damage leading to degeneration. A variety of antioxidant tests have been used but, since damage to the lipids in the cell wall is thought to be a major process contributing to neurodegeneration, a test using thiobarbituric acid to measure the amount of malondialdehyde (MDA) formed as a result of oxidative damage of liposomes, can be considered as a reliable model and has been used extensively.

Since inflammation is also considered to be a causative factor of neurodegeneration, the effects of extracts of plants used traditionally to treat elderly people on enzyme systems linked to inflammation has also been an approach that has been taken. Most studies have utilised cyclo-oxygenase or 5-lipoxygenase as targets for inhibition since this decreases the amount of pro-inflammatory eicosanoids (e.g. prostaglandins and leukotrienes) produced. Inflammation is a complicated process and the use of pathways leading to other contributory compounds has not been very extensive.

It should be noted that activity displayed in tests based on cells or enzymes is no guarantee that the extract or compound will be of value therapeutically, because of factors associated with absorption, distribution, metabolism and excretion, as well as safety, which might invalidate candidate compounds showing activity in reductionist assay systems. At best a battery of *in vitro* tests should be used but even then, extrapolation of *in vitro* tests to an *in vivo* situation has to be treated very cautiously.

1.4. Plants as a source of useful therapeutic agents in neurodegenerative diseases

The major plants and their constituents which have played a role in current therapy for the neurodegenerative diseases AD and PD, either in mainstream medicine or as complementary 'herbal' medicine, are discussed in detail below, with particular reference to ethnopharmacological aspects. In both conditions, some compounds in use are found in plants used in traditional medicine and others have been designed using an active molecule of interest which is a natural product.

The plants mentioned below are mainly those arousing interest in the scientific 'Western' community. It should not be forgotten that there are many other traditional medicines consisting of unextracted plant material or crude extracts which have shown interesting activity in test systems but which have not been investigated further. Some of these have been publicised widely as 'alternative' treatments but it must be stated that, in many instances, the evidence for efficacy and safety is not very substantial. This latter group may well contain compounds which are more active when combined in a mixture than when isolated and used alone and so the use of an extract may be preferable to single isolated constituents. In addition, in a mixture, such as an extract, there may be a variety of compounds with polyvalency i.e. different, but relevant, pharmacological effects which provide a multi-pronged approach to treating the condition.

2. Plants and their constituents from Ayurvedic medicine

Ayurvedic medicine is the oldest medical system in the world with written records in Sanskrit stretching back for at least 5000 years. It originates from the Indian subcontinent and has also influenced the traditional medical system in Thailand. It is now widely practised throughout the world as a complementary medicine.

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Biographical Sketches

Peter Houghton has been Professor in Pharmacognosy at King's College London since 1999, where he has been teaching and conducting research since 1971. His research group is the largest of its type in the UK and he has published over 200 articles dealing with the ethnopharmacology, chemistry and biological activity of plants and other natural substances. His major research interests are natural products and extracts for the treatment of neurodegenerative disease, as treatments for cancer and for wound-healing. Most of his research is based on ethnopharmacological information.Professor Houghton was instrumental in setting up the Kew-Kings-Square Phytochemical Group which meets regularly and fosters collaboration between the three research groups with the result that London is now the major centre in UK for medicinal plant research. Professor Houghton is a member of the committee of several international scientific groups interested in medicinal plants and is currently President of the International Society of Ethnopharmacology. He is also an Assistant Editor of the Journal of Ethnopharmacology. He has extensive international contacts through students and visitors who have worked in his laboratory and has travelled widely to give lectures, to collaborate in research and to consult on course development in teaching about natural products in the syllabus for pharmacy at undergraduate level.

Dr Melanie-Jayne Howes graduated in pharmacy from King's College London in 1996 with First Class Honours, winning prizes in 1995 for 'Scientific basis of therapeutics' and for being the top student, and winning prizes in 1996 for 'Clinical pharmacy' and for being the top student, in addition to receiving the highest marks in the final year pharmacy elective subjects 'Plants and pharmacy' and 'Drug discovery from natural sources'. While completing her pre-registration year, she was awarded a scholarship from the Royal Pharmaceutical Society of Great Britain to fund a PhD. After registering as a pharmacist in 1997, she began a PhD titled 'Chemistry and biological activity of plants with traditional uses relevant to Alzheimer's disease' in the Department of Pharmacy at King's College London. During this time, Dr Howes also worked as a pharmacist in community pharmacy. Following the successful completion of her PhD in 2001, she was awarded the prize for the best thesis in the Department of Pharmacy.In 2001 Dr Howes began a post-doctoral appointment at the Royal Botanic Gardens, Kew, where research has focused on authentication and quality control aspects of plant material. During this time, she also lectured to MPharm IV students in pharmacognosy and phytochemistry at the Department of Pharmacy, King's College London. Research from her PhD and from quality control investigations at Kew has been

published, and has been presented at several conferences, including internationally. In addition, Dr Howes has also co-authored some review papers and book chapters relating to the management of Alzheimer's disease and other cognitive disorders using plants and phytochemicals.