The Future of **Dementia Therapies?**

Professor Hiroaki Oguro

Scientia

THE FUTURE OF DEMENTIA THERAPIES?

Efficacy of Ferulic Acid for the Treatment of Dementia

Associate Professor Hiroaki Oguro and his colleagues at Shimane University study the effects of plant antioxidants on dementia symptoms. Specifically, Professor Oguro is interested in the effect of Ferulic Acid on cognitive and behavioral symptoms of dementia in humans.

Dementia

Dementia is the progressive decline in cognitive abilities. The most common form is brought on by Alzheimer's disease (AD). However, vascular dementia, dementia with Lewy bodies and frontotemporal lobar dementia have also been identified. Cognitive impairments initially occur in one of the following categories: memory, executive functioning (processes related to planning, attention and multitasking), language, visuospatial abilities or personality and behaviour. However, as the disease progresses, impairments may be observed in multiple categories. In addition to difficulties concentrating, focusing and memory loss, dementia may also result in lack of motivation, depression, delusions or hallucinations, sleeping difficulties and muscle weakness. Behavioural and psychological symptoms of dementia may also occur. These include delirium, anxiety, apathy, low activity and agitation. Dementia typically occurs after the age of 65 (although there are cases of early onset), and the risk for dementia increases with age. Life expectancy ranges from 3 to 12 years following the time of onset.

Alzheimer's disease

Alzheimer's disease (AD) is the most common progressive neurodegenerative disorder, and the cause behind the majority (75%) of dementia cases. Alzheimer's disease is characterized by the accumulation of senile plaques (deposits of protein fragments called amyloid beta (Aß) in the brain), neurofibrillary tangles (aggregates of phosphorylated tau protein) and nerve cell (neuron) degeneration. The plaques are generated from improper cleavage of a protein known as the Amyloid Precursor Protein (APP). APP is located on the surface of cells. In the healthy brain, APP is cleaved by ß- and y- secretase enzymes, which releases 40 amino acid long protein fragments. However, in the case of Alzheimer's disease, APP is cleaved improperly by ɑ- and y-secretase resulting in 42 amino acid long fragments. These fragments accumulate and form senile plaques. These plaques also make up the Lewy Bodies in dementia with Lewy bodies. Amyloid plaques contribute to neuron degeneration and dementia by disrupting normal cell behaviour and cell signalling and generating oxidative stress – a process resulting from the accumulation of free radicals and other reactive oxygen species resulting in cell damage. Therefore, a treatment that reduces or reverses plaque formation may provide a way to prevent or cure dementia in the future.

Current Therapies for Dementia

Although there is currently no cure for dementia, there are treatments available to improve dementia symptoms. Acetylcholinesterase inhibitors (medications that prevents the breakdown of a chemical messenger in the brain involved in cognition) and memantine (a drug used to prevent overstimulation of neurons, a process which can cause cell death) are the only therapies approved by the Federal Drug Administration to treat dementia. A combination of acetylcholinesterase inhibitors is used as a first-line therapy to treat mild and moderate dementia in patients with Alzheimer's disease. Memantine is only used when patients are not able to tolerate the side effects of inhibitor therapies.

While these treatments moderately improve cognition, they have several drawbacks. One concern is that they are only approved to treat specific forms of dementia. In some cases, these treatments may even worsen symptoms. Potentially severe side effects are also associated with inhibitor therapy. Behavioural and psychological symptoms of dementia can be treated with antipsychotics. However, these treatments also have side effects. Lastly, these treatments can also be very expensive for the patients. The limited options and severe side effects have made the development of new, more effective and safe therapies crucial for the treatment and eventual cure of dementia. It is this lack of adequate, tolerable and affordable therapies that has driven Professor Hiroaki Oguro and his colleagues to explore alternative treatments for dementia. 'For dementia there are very few drugs available in the world. Only three cholinesterase inhibitors and memantine are widely used.' he told us. Recently, Professor Oguro and his lab have focused their attention on a plant antioxidant supplement that has several therapeutic benefits.

'For dementia there are very few drugs available in the world. Only three cholinesterase inhibitors and memantine are widely used.'

Oxidative Stress and Antioxidants

Oxygen is the main provider of energy in the body. One of the by-products of its conversion into an energy source is reactive oxygen species (ROS). Related reactions in the body also produce reactive nitrogen species (RNS). In low and moderate amounts, ROS and RNS can have several beneficial effects. They contribute to cell signalling and immune functions. However, in high concentrations, resulting from either an increase in reactive specie production or a decrease in antioxidant concentration, ROS and RNS can cause oxidative stress, a process that has deleterious effects on cell structures and function. This includes DNA and protein damage, formation of tears in the cell surface and even cell death. Several diseases including dementia-related conditions are aggravated or initiated by an accumulation of ROS. In the case of Alzheimer's disease, the cell damage caused by the reactive species contributes to the deterioration of regions of the brain essential to memory, emotional behaviour and executive functions.

To combat the accumulation of free radicals and other reactive species, antioxidants bind to free radicals to prevent them from interacting with cell structures and causing additional damage to the cell. These are usually obtained from plant-based foods, although meat and minerals can have similar effects on reducing free radicals. Because free radicals play such a basic role in disease onset and progression, Professor Oguro has become increasingly interested in using antioxidants as potential therapeutics for today's most severe diseases.

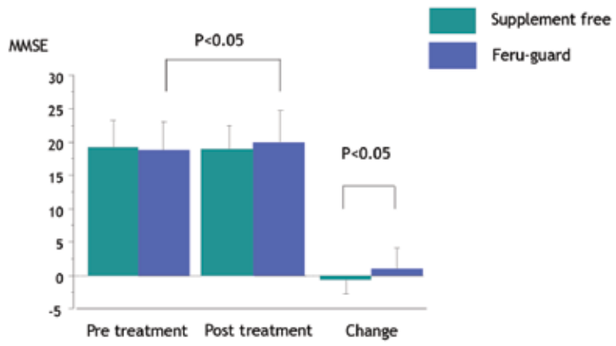
Ferulic Acid

A promising group of antioxidants are phenols. Phenols are organic compounds largely produced by plants

and microorganisms (Although, synthetic phenols can also be made). Phenols are best known for their therapeutic effects on a wide range of diseases including neurological, cardiovascular, metabolic, inflammatory and age-related ailments. Because of their abundance, they are a significant part of the human diet. They are not only beneficial in protecting against disease, but also viral and bacterial infections and allergic reactions. Once inside the body, phenols perform many different protective actions such as interact with free radicals to reduce oxidative damage, bind to harmful metals, influence enzyme activity, and even activate gene expression. While synthetic phenols are capable of similar therapeutic functions, naturally occurring phenols are preferred because they contain natural components that are more likely to be compatible with the human body.

Of particular interest to Professor Oguro's research team is the phenol known as 4-hydroxy-3-methoxycinnamic acid, or ferulic acid (FA). Like many phenolics, FA is a naturally occurring antioxidant abundant in plant leaves and seeds of fruits and vegetables. FA has unique properties that make it a particularly potent antioxidant. It has the ability to stop free radical chain reactions that continuously produce new reactive species, and also contains several sites for reactive species to bind to, thus preventing them from attacking host cells. Lastly, FA can attach to the surface of cells and protect them from oxidative damage. FA functions to protect plants from harmful enzymes during germination, regulates plant growth, contributes to mineral and water absorption in the roots and protects the plant from competing plants in its environment. However, its benefits extend past plants. FA's ability to bind to and stabilise free radicals has translated into a wide range of therapeutic effects for humans including anti-diabetic, anti-inflammatory, anti-cancer and neuroprotective effects.

Another beneficial attribute of FA is that it is highly bioavailable, meaning that a high percentage of FA reaches the diseased or injured site after it is administered. Many substances are broken down after administration and so only a small percentage reaches the injured tissue. However, FA is one of the most bioavailable phenols studied. Thus, small doses of FA will have a large medicinal effect. This also minimises the chances of side effects.



The effects of Feru-guard on MMSE in 35 dementia patients. MMSE: Mini-Mental State Examination

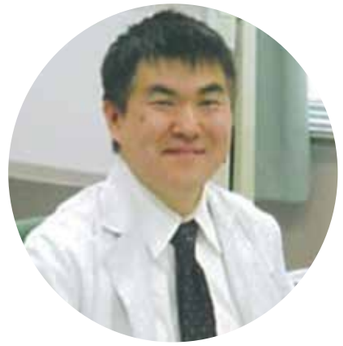
Ferulic Acid and Alzheimer's Disease

There is some evidence suggesting that FA may also be beneficial in treating Alzheimer's disease. A recent study found that treatment with FA blocks amyloid plaque formation, prevents plaque expansion and destabilises plaques that had already formed. Animal models of Alzheimer's disease involving mice with amyloid plaques in their brains also revealed that FA treatment prevented the progression of learning and memory deficits brought on by the disease. It is thought to stave off further deterioration of vital cognition related brain regions by preventing amyloid plaque originating free radical-induced changes in proteins on the cell surface involved in neuron signalling. Long term administration of FA has also been shown to prevent activation of microglia – the nervous system's immune cells. These cells can be activated by amyloid plaques and may contribute to neurofibrillary tangle development in Alzheimer's disease. In addition, FA activates protective genes and proteins in regions of the brain involved in memory.

Ferulic Acid Improves Dementia Symptoms

The multipronged approach of FA in treating symptoms of Alzheimer's disease, as well as its high abundance and inexpensive cost, have driven Professor Hiroaki Oguro and his team to further explore the effect of ferulic acid on dementia. To do this, Professor Oguro launched a clinical study to investigate the effects of a ferulic acid supplement on patients with various types of dementia. Study participants were patients with dementia (Alzheimer's Disease, frontotemporal lobar degeneration, vascular dementia or dementia with Lewy bodies) that experienced progressive cognitive decline and memory impairment. Patients were treated with a supplement known as Feru-Guard® (GLOVIA, Tokyo, Japan). Feru-Guard is a food supplement consisting of FA extracted from rice bran and garden angelica – a biennial plant commonly used as a flavouring or medicinal agent. Feru-Guard was taken twice a day for 6 months. These 6 months were either preceded or followed by another 6 months without treatment. Memory, visual attention and behavioural and psychological symptoms of dementia were assessed after each 6-month period.

The results of the study are very promising. Professor Oguro concluded that treatment with the supplement did in fact improve memory performance, Mini-Mental State Examination (MMSE). And while treatment did not improve visual attention (Trail Making Test-part A: TMT-A), it did prevent further decline in attention (TMT-A). These results suggest that Feru-Guard may have beneficial effects on some of the memory and cognitive impairments resulting from dementia in humans. Based on these findings, Professor Oguro and his lab are now looking at the effect of FA in milder cases of dementia and cognitive impairment in a new clinical trial. Enrolment of new patients is nearly complete.



Meet the researcher

Professor Hiroaki Oguro
Associate Professor
Department of Neurology
Shimane University
Japan

Professor Hiroaki Oguro is an associate professor in the Department of Neurology at Shimane University. He received his medical degree from Shimane Medical University and subsequently joined their Department of Neurology. In the next two years, he trained as an intern in internal medicine at Shimane Medical University Hospital. He then went on to obtain his PhD in Medical Science from Shimane Medical University. In 2002, he was appointed Assistant Professor. After serving a year as a visiting research fellow at Wales University Bangor in their Cognitive Neuroscience Laboratory, he was appointed to his current position as Associate Professor in 2007.

CONTACT

E: oguro@med.shimane-u.ac.jp
T: (+81) 853 20 2199
W: http://www.shimane-u-internal3.jp/

KEY COLLABORATORS

Ryo Mizuhara, MD, Shimane University
Chizuko Hamada, MD, Shimane University, Shimane Medical Center for Dementia
Satoshi Abe, MD, Shimane University, Shimane Medical Center for Dementia
Hiroyuki Takayoshi, MD, Shimane University
Shingo Mitaki, MD, PhD, Shimane University
Tomonori Nakagawa, MD, Shimane Prefectural Central Hospital
Keiichi Onoda, PhD, Shimane University
Yoko Kuroda, OT, Shimane Medical Center for Dementia
Atsushi Nagai, MD, PhD, Shimane Prefectural Central Hospital
Shuhei Yamaguchi, MD, PhD, Shimane University, Shimane Medical Center for Dementia

FUNDING

Glovia Co. Japan
W: http://www.glovia.co.jp/