Remarkable retinoids

Although there is much to be learnt about the role of retinoids in many biological functions and their potential use as therapeutics, Dr Hiroshi Fukasawa explains how these potent compounds could represent a likely candidate for the treatment for Alzheimer’s disease.
New therapeutics for Alzheimer’s disease

With the prevalence Alzheimer’s disease on the rise, innovative therapeutic options are urgently needed. Scientists at the Research Foundation ITSUU Laboratory in Japan are investigating retinoids, which could prove fruitful in enhancing learning and improving memory performance amongst patients.

ALZHEIMER’S DISEASE (AD) is a growing socioeconomic problem as average life expectancy increases, particularly in developed countries. Affecting mainly elderly individuals, the aetiology of AD is complex, and the cause of early onset AD also remains unclear. Genetic and environmental factors, as well as infection, may play a role and a variety of factors may also contribute to the progression of the disease. Due to this complexity, it is postulated that multi-target therapies may prove to be more effective than single-target therapies in limiting the onset and progression of AD.

Drugs currently used to treat AD are neurotransmission modifiers, which only work to ameliorate symptoms. With the emergence of findings linking amyloid (Aβ) plaque formation in the brain to AD, anti-Aβ therapies, designed to reduce Aβ production or promote Aβ clearance, have been proposed.

Recent research has shown that tau protein and mitochondrial dysfunction may also be potential targets for therapy. One possible approach could be the use of multi-drug therapies, with each drug having a different target. Another possibility could be the use of a single drug that acts on a range of targets such as Aβ, inflammation and neurotransmission, involving different pathways or physiological categories.

RETINOIDS

Led by Dr Hiroshi Fukasawa, a group of researchers at the Research Foundation ITSUU Laboratory in Tokyo are currently investigating the potential of retinoids as candidates for use in AD. Retinoids are analogues of all-trans-retinoic acid (ATRA), an active metabolite of vitamin A (retinol) and have a number of important roles in the growth and development of vertebrates, maintenance of the immune system, and the development and regeneration of the nervous system. They directly regulate a number of key genes and proteins in diverse pathways, and their principal biological targets include neurotransmission, Aβ, inflammation and neurogenesis and the blood-brain barrier.

Retinoic acid receptors (RARs), the nuclear receptors for retinoids, transduce retinoic acid into biological action through the transcriptional control of target genes. The nervous system expresses RAR, of which three subtypes (RARα, β and γ) have been identified thus far, in a spatially and temporally controlled fashion. The essential roles of RAR in normal neural development during embryonic stages have been well-studied, but even though their roles in the adult brain remain poorly understood, many studies suggest that retinoids are involved in normal learning/memory and neural regeneration. Fukasawa enthuses: “Retinoic acid should be recognised as an essential hormone for life, as steroid hormones are. The clinical application of retinoids in neurodegenerative diseases such as AD is a new frontier in retinoid biology and a topic of social significance”.

TAMIBAROTENE

In Japan, a synthetic RARα/β agonist called tamibarotene (Am80) has been developed for the treatment of acute promyelocytic leukemia (APL). Tamibarotene has been shown to have transcriptional controls of multiple target genes involved in the aetiology and pathology of AD, and is therefore considered to be a promising candidate drug for its treatment. Fukasawa’s team and others have demonstrated in animal models that the administration of tamibarotene decreased the deposition of insoluble Aβ; ameliorated the decrease of cortical acetylcholine; reduced inflammatory cytokines; improved the recovery of spinal cord-injuries; reduced anxiety in behavioural tests; improved sleep deficits; and effected a significant improvement of memory. Tamibarotene may also improve vascular factors involved in the onset and/or progression of AD.

In previous research by another group, TTR, a carrier protein of retinol necessary for its transport into the brain, was shown to be significantly lower in AD patients than in non-dementia control individuals. It was also shown that plasma TTR is significantly lower in rapid decliners than in non-rapid decliners in AD patients, and significantly lower in moderate to severe AD patients than in mild AD patients. Therefore, it is likely that low plasma TTR levels may cause insufficient production of retinoic acid from retinol in the brain, thereby accelerating the progression of AD. Thankfully, tamibarotene can penetrate into the brain without the help of TTR.

Many studies suggest that retinoids are involved in normal learning/memory and neural regeneration.
INTELLIGENCE

RETINOIDS HAVE A LEARNING FUNCTION ENHANCING ACTIVITY

OBJECTIVES
To determine if retinoids provide a novel approach for treatment of Alzheimer’s disease.

KEY COLLABORATORS

Professor Hiroshi Katsuki; Dr Kohichi Kawahara, Kumamoto University, Japan
Dr Kazuyoshi Kitaoka, University of Tokushima, Japan
Professor Kagechika, Tokyo Medical and Dental University, Japan
Professor Takami Miki, Osaka City University, Japan
Professor Fumihiko Yasuno, Nara Medical University, Japan

FUNDING

Grant-in-Aid for Scientific Research (KAKENHI) from the Japan Society for the Promotion of Science

CONTACT

Dr Hiroshi Fukasawa
Senior Scientist
Research Foundation ITSUU Laboratory
2-28-10 Tamagawa Setagaya-ku Tokyo 158-0094 Japan
T +81 3 3700 5493 E hfukasawa@itsuu.or.jp

HIROSHI FUKASAWA received his PhD in Pharmaceutical Science from the University of Tokyo in 1992. After working as a member of the teaching staff in Professor Shudo’s lab, he joined a drug discovery company, IMMID Inc., in 2001. He later worked in Professor Shudo’s lab as Senior Director of the Drug Discovery Research Division. He moved to ITSUU laboratory in 2012.

CLINICAL TRIAL AND APPLICATIONS

Fukasawa’s team commenced a clinical study to evaluate the efficacy and safety of tamibarotene to examine the use of tamibarotene for treatmen of AD as tamibarotene has been in clinical use for the treatment of APL in Japan since 2005, and has been reported to have fewer and milder side effects than other retinoids. His group is planning to use stratification sampling for future clinical trials, selecting patients for recruitment who lack enough retinoic acid in the brain due to decreased plasma transthyretin (TTR) levels. It is hoped that the outcome of the trial will mark a breakthrough in understanding of the clinical application of tamibarotene by the researchers, which may also unlock new avenues of research.

Tamibarotene therapy has potential to be used for other neurodegenerative diseases. Candidate applications include: Parkinson’s disease, where the increase of dopamine transmission by retinoids may be helpful; multiple sclerosis, an autoimmune disease of the brain where the involvement of retinoic acid in the suppression of autoimmunity could benefit patients; and spinal cord injury, for which RAR may promote neural outgrowth and neurogenesis. Because tamibarotene is rapidly excreted from the body and hardly accumulates in the brain, it is easy to control efficacy and adverse events. Also, dermal toxicity commonly observed in retinoids is much less frequent in tamibarotene because it lacks affinity with RARγ.

PARTNERSHIPS OF SUCCESS

Fukasawa is partnering with a number of other laboratories in Japan on this project and is working with many leaders in the field, including Professor Hiroshi Katsuki and Dr Kohichi Kawahara at Kumamoto University, Dr Kazuyoshi Kitaoka at the University of Tokushima, Professor Hiroiuki Kagechika at Tokyo Medical and Dental University and Professor Takami Miki at Osaka City University. Looking to the future, he also intends to progress international collaboration with overseas scientists.

An important industrial partner for Fukasawa’s research is the pharmaceutical company Toko Pharmaceutical Industries. Tamibarotene/Am80 is now commercially available thanks to the industrial partnership, which enabled the development and manufacture of GMP-grade tamibarotene tablets for the treatment of refractory APL, and the first clinical trials of Am80 for APL in China.

At present, Miki is leading ongoing pilot clinical trials at several sites across Japan to prove the efficacy and safety of tamibarotene in mild to moderate AD patients. This involves an interventional, randomised, placebo-controlled study, in which patients receive two tamibarotene 2 mg tablets, provided by Toko Pharmaceutical, or two placebo tablets once daily for 24 weeks. Severe adverse events have not been reported. The trials are currently small-scale due to budget constraints but Fukasawa plans to focus his efforts on promoting these clinical trials and sourcing funding for larger clinical trials to further explore the untapped benefits of tamibarotene for AD sufferers.

References


For additional information please also refer to http://www.itsuu.or.jp/en/alzheimer.html