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Cognitive Health:

MIND THE GAP

Vitafoods™ INSIGHTS

CONTENT

September 2017

Diving Head First into Cognitive Health

Some consumers want to enhance their memory, others want clarity, others just want to ensure they are 'feeding their brains' with whatever is good for them—like the old adage about fish being 'brain food'. Consumers expect to live longer than previous generations and they are doing what they can to ensure those additional years are productive and fruitful.

Surprisingly, though, it's been difficult to market cognitive health products to younger consumers as part of a healthy lifestyle, likely because different generations are searching for different effects from their brain health products. Seniors want to enhance their memory and preserve cognitive function, and realise they need to address the changes associated with the ageing experience; millennials are focused on alertness and mood as progressively more stressful lives prompt an increase in sleep disorders, anxiety and low mood; and parents want the best for their growing infants, with a mature category offering products for the developmental aspects of cognitive health.

Join me as I investigate the cognitive health market globally, starting on page **4**, and explore the consumer trends, popular ingredients and innovation shaping the brain health sector.

The brain undergoes pronounced structural changes in old age and recent findings suggest improving the diet of older people might help to delay cognitive ageing. This research is crucial, as the number of people living with dementia worldwide is expected to double every 20 years. Anastasia Smith, communications manager at Food for the Brain, details the nutritional approach necessary to take control over cognitive health and wellbeing, on page **11**.

To evaluate the effects of nutraceuticals on brain health and elucidate the underlying mechanisms involved, new testing models and techniques are available. Francois Roman, Johann Meunier and Vanessa Villard, scientific board members from Amylgen, examine the many services developed to reproduce the brain ageing process, starting on page **16**.

It's been said, to ensure a healthy brain, choose your parents wisely; maternal prenatal and infant nutrition have a greater impact on long-term brain health than choices made later in life. Today's consumer knows differently—many natural ingredients can help delay or even prevent neurological decline and preventative measures are vital to lifelong cognitive health.

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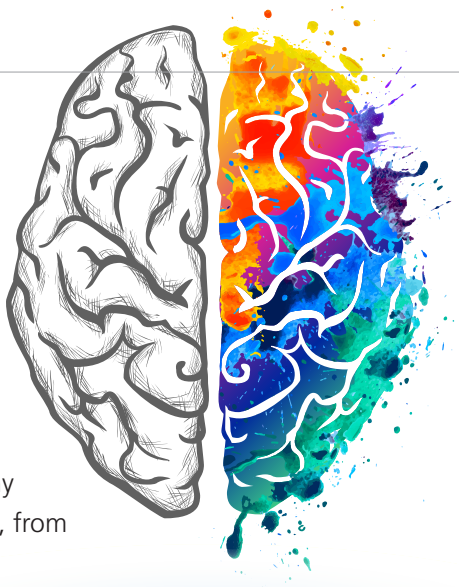
Mind Your Own Business



by Jade Mitchell-Ross

As the world population ages, the traditional assumption is cognitive health concerns are reserved for the elderly. Today's consumer knows differently—cognitive health is a staple of healthy ageing as a vital component of good health throughout a lifetime, from development in the womb to old age.

Age-associated cognitive decline—or normal (non-pathological) cognitive ageing—is an important human experience which differs in extent between individuals. While some mental capabilities are maintained into old age, from early adulthood, some declines in processing speed, reasoning, memory and executive functions can be expected; some of these are underpinned by a decline in general cognitive function.

Various factors make every person's cognitive ageing personal: genetics, medical disorders, inflammation, neurobiological changes, and, importantly, diet and lifestyle.

Traditionally, it has been difficult to attract consumers to cognitive health products before their older years, when the expectation and symptoms of mental decline typically surface. One of the biggest challenges has always been engaging consumers to understand the role of targeted products in maintaining and preserving brain health and cognitive function as part of a healthy lifestyle, and not just as a quick fix or a staple of the senior's lifestyle. According to Natural Marketing Institute's (NMI) Health and Wellness Trends Database[1], nearly 60 percent of consumers are concerned about brain health.

Seniors

Cognitive impairment is becoming a major health and social issue across nations as the global population ages. An article in the December 2009 British Medical Bulletin[2] named cognitive decline as the most feared aspect of growing old—and also the most costly, in terms of the financial, personal and societal burdens. In the United Kingdom, cognitive failure is the cause for 40 percent of elderly admissions to institutional care.

The brain undergoes pronounced structural changes in old age, including a steady decrease in brain size. Brain atrophy accelerates in old age; however, studies suggest associations between structural brain differences and cognitive ability tend to be modest[3-5]. The roles of diet and other lifestyle factors are attracting increasing scientific and consumer interest. Recent findings suggest improving the diet of older people might help to delay cognitive ageing and current research focuses on the role of specific natural ingredients.

Research supports the importance of a diet rich in B-vitamins, antioxidants and omega-3s. B-vitamins are essential for maintaining normal brain function and memory, particularly vitamins B12, B6 and folate (B9). Oxidative damage has been implicated in cognitive ageing,

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and evidence from cross-sectional studies supports a link between antioxidant status and cognitive function in older people[6]. Omega-3s have well-established brain health benefits and docosahexaenoic acid (DHA) is particularly highly concentrated in the brain. Habitual consumption of oily fish later in life is associated with a reduced risk for cognitive decline and dementia[7,8]. Scientific opinion considers the Mediterranean diet especially beneficial for cognitive abilities in old age, while a diet high in refined sugars, cholesterol and trans-fats might be associated with poorer cognitive outcomes in older adults[7].

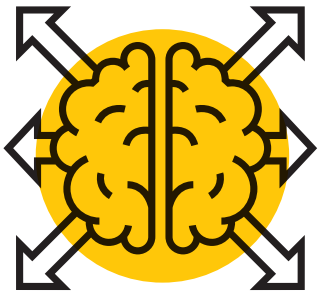
Research supports the importance
of a diet rich in B-vitamins, antioxidants and omega-3s.

According to data from Acute Market Reports[9], the memory enhancement sector was the largest cognitive health sector in 2015, and is predicted to remain on top during the forecast period of 2016 to 2024. It is estimated 46.8 million people throughout the world currently suffer from dementia, with the overall number predicted to double every 20 years. The global direct and indirect costs associated with Alzheimer's disease and other forms of dementia is estimated to be €211 billion. While the brain health category can expect to grow over the next few years, it remains to be seen how delivery formats develop from traditional supplements to functional foods and beverages. There are few brain health foods targeted specifically at older people to date, with many, especially those fortified with omega-3s, focus on products for children. This is a key opportunity for industry growth.

Millennials

Deepening understanding of the role of nutrition and select bioactives to support or enhance cognitive function has led to a growing number of dietary supplements and functional products focusing on attention and alertness to memory and mood. These are popular categories among the younger generation searching for a 'brain boost'—students look for memory enhancers, young adults want to feel more alert, and one in five millennials has reported experiencing depression, according to research from Bensinger, Dupont and Associates[10].

The progressively more stressful lives led around the world have prompted an increase in remedies to treat sleep disorders and anxiety, according to market research firm SPINS[11], with the segment expanding by more than 35 percent. While serious mental health issues have long been the territory of pharmaceuticals, people suffering from milder forms of depression or anxiety can benefit from nutrients that can help balance mood—it is reported 31 to 68 percent of people with depression have a nutritional deficiency[12]. Dietary supplements and functional foods with mood-enhancing benefits, such as L-theanine, could make significant

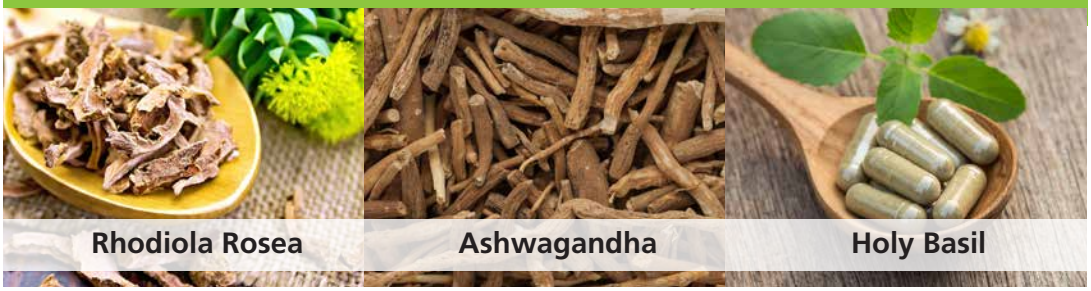


Products focusing on mood and alertness are popular
among the younger generation searching for a '**brain boost**'

gains, especially those with research-backed, proven claims of efficacy. However, there are currently no EFSA approved health claims for mood boosting ingredients.

Adaptogens are becoming increasingly popular, particularly in the United States, and are understood to help the body adapt in times of mental stress—they help bring the body into equilibrium, and are a staple of Ayurveda, which is based on the health and healing concept of balance and harmony in the body. Adaptogenic herbs include Rhodiola rosea, ashwagandha, and Holy basil. Though many adaptogens are well researched, they are yet to enter the European market with any noticeable impact. With the regulatory environment as it is in Europe, the only widely available herbal product with adaptogenic properties is ginseng. As research shows Rhodiola rosea and ashwagandha can help balance mood and stress levels, and stress is a growing concern in the European Union[13], there is potential for adaptogens, if manufacturers can navigate successfully through the regulatory maze.

Adaptogens are becoming increasingly popular



Cannabidiol (CBD) is an intriguing prospect as a brain health ingredient. Anxiety issues are major drivers of medical marijuana prescriptions, and preliminary studies show CBD may have neuroprotective benefits. Europe is set to be a key market for new cannabinoid-infused nutraceutical products targeting the nutrition industry, although the European Industrial Hemp Association (EIHA) has said there's an 'urgent need' for 'proper legislation'. Data from Mintel shows global food and drink product launches with a hemp ingredient jumped from 12 percent in 2009 to 29 percent in 2013. Although EIHA says medium doses of CBD should be available to buy as herbal medicines or food supplements, without prescription, manufacturers do face regulatory hurdles.

Many consumers seeking mental acuity look to coffee, one of the world's most popular beverages and stimulants. There are other natural ingredients to turn to, such as Bacopa monnieri, Citicoline and Ginkgo biloba. When positioning a dietary supplement for alertness and attention, consumer education and appropriate marketing are vital to ensure consumers don't have false expectations—many consumers are looking for an immediate energy boost similar to taking caffeinated products. While only one in four young adults drinks coffee, according to a report from Fortitech Premixes[14], seven out of 10 elderly people are coffee drinkers. With the ever-increasing demographic trends towards an elderly population, the underlying market demand for cognitive boosting products is bound to increase substantially in the future.

1 in **4**
young adults
drinks coffee

7 out of **10**
elderly people are
coffee drinkers

Infants

Despite increasing interest in cognitive health from the ageing population, the majority of new product launches globally are baby foods, particularly infant formula, where DHA is often incorporated for its brain development properties[15]. The first 1,000 days of a child's life—from conception to their second birthday—present a critical opportunity where nutrition can play a key role in developing a child's long-term health and wellbeing, and both parents and the industry are taking note.

Manufacturers focus on brain growth, rather than optimisation, with product compositions including nutrients vital to ensuring healthy brain development and function. Women looking to become pregnant are encouraged to start taking omega-3 and folic acid supplements up to six months prior to conception, and should continue to do so through pregnancy and while breastfeeding. A survey into maternal supplement usage behaviour by DSM Nutritional Products found supplement intake peaked during pregnancy and very early motherhood, with 87 percent of respondents reporting consumption of vitamin supplements or fortified products while pregnant, and 75 percent purchasing in the first six months post-partum.

> **Both iron and omega-3 fatty acids** are also crucial components for maternal health.

Iron requirements are very high, as the infant's body and blood volume grow rapidly, and the brain will not be prioritised in an iron-deficient child, which could lead to cognitive and behavioural problems later in life[16]. DHA is critical for neurological and visual development in infants—during the last trimester and the first two years after birth, infant brain development is at its most rapid and complex, and the child's neurological development is dependent on the dietary intake of essential nutrients, especially DHA[17-19]. Both iron and omega-3 fatty acids are also crucial components for maternal health. Pregnant women are at increased risk of anaemia due to high foetal iron requirements, and a high omega-3 index level is important at all stages of life. Other nutrients include choline for brain cell membrane development and folic acid to prevent spinal tube defects.

As pill fatigue is a common complaint among pregnant women, there is a market for alternative delivery formats, and the women surveyed by DSM were found to favour soft chews and emulsions as new supplement concepts. There is an untapped demand for products developed specifically for pregnant women and new mothers, particularly for fortified foods and beverages, which are not currently common on the European market.

Looking Ahead

Cognitive health is increasingly being considered and marketed as a long-term nutritional investment for the consumer. While many natural ingredients can help manage the symptoms of severe neurological disorders, there is no magic pill solution—thus preventative measures are vital to lifelong cognitive health.

As industry sees the blurring of categories in sports nutrition, there is opportunity for the same in cognitive health products. Research has uncovered a 'delicate relationship' between the circulatory system and the brain, which, if upset by vascular disease, 'may affect normal brain functioning'[20]. Although few studies have examined cognitive defects in patients with mild coronary heart disease symptoms, poorer mental status, memory and executive functions have been reported in survivors of acute myocardial infarction[20]. In population-based studies, elderly people with peripheral arterial disease have an increased risk of progressive cognitive decline, particularly in verbal memory, which cannot be explained by other risk factors[21]. Various studies have also associated inflammation with cognitive decline[22]. There are myriad opportunities for cross-category new product formulation and with consumers leaning towards on-the-go, single-dose formats, this is an area of the market ripe for development.

Euromonitor International found global sales of cognitive health dietary supplements reached €426 million in 2013[23], and as the global population ages and awareness of cognitive health benefits increases, future growth in this market can be expected. Evolving research, a growing population at risk of neurodegenerative diseases, and consumers' desire for prevention at an earlier age will continue to advance the brain health sector. Acute Market Reports data shows[24], in 2015, North America was the largest regional market for brain health supplements, accounting for more than half the total market share. The data suggests strong desire to enhance brain function among the adult population, the large Boomer demographic, and availability of quality products are driving the market growth in North America. Asia Pacific is expected to project the highest growth throughout the forecast period, due to high populations, rising foreign investment, economic development and increasing consumer awareness across the middle classes.

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The Important Role of Nutrition in the Prevention of Alzheimer's

by Anastasia Smith

Memory loss, poor concentration and depression are common early signs and symptoms of dementia, which can be frightening and very isolating for those experiencing them. Every year, 21st September is officially dedicated to Alzheimer's Awareness across the globe, with a large number of charities and organisations campaigning to raise awareness about this neurodegenerative condition.

There are an estimated 46.8 million people worldwide living with dementia and this number has been predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 20501. In the UK alone, 1 in 14 people over 65 have Alzheimer's disease[2], a form of dementia which accounts for around two-thirds of all dementia cases. A lot of public communication on dementia has led many to believe there is nothing that can be done about this disease until a pharmaceutical cure is found, and dementia is somehow inevitable and 'in the genes'. However, research to date shows only 1 percent of the risk of Alzheimer's is actually caused by genes and up to 50 percent is attributable to modifiable diet and lifestyle related factors[3]. With these figures looming, it is crucial there is more awareness generated on taking a positive approach to preventing dementia and the symptoms that come with it. Prevention is an area which is not spoken about enough; since 2008, less than 1 percent of funding has been spent on prevention research[4]. Funding has been largely focused on finding medication to treat dementia rather than its prevention. However, the recent research for drugs has been fruitless—there is no medication to slow the disease process in Alzheimer's and because of this, many people feel that there is nothing they can do to help themselves or help their family members.

In the UK alone, 1 in 14

people over 65 have Alzheimer's disease,
a form of dementia which accounts for around two-thirds of all dementia cases.

As a charitable foundation, with a mission of generating awareness about the importance of nutrition for cognitive and mental health, our aim at Food for the Brain is to promote a more proactive message, providing positive steps we can all take to reduce our risk and give back a sense of control over cognitive health and mental wellbeing. As part of the Take Positive Action

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on Alzheimer's campaign, we have developed a free online Cognitive Function Test which aims to help people self-assess their level of cognitive health and potential risk of Alzheimer's disease. In addition to the test, there is a diet and lifestyle questionnaire, which details steps one can take to improve their brain function. To give people the best support possible, we have developed a guide that promotes the importance of six essential diet and lifestyle steps, which have been shown to help prevent the risk of developing Alzheimer's. These steps include eating foods rich in antioxidants, increasing intake of omega-3 rich foods, supplementing with B vitamins, eating a diet low in glycaemic load, limiting caffeine and alcohol, and keeping physically, mentally and socially active.

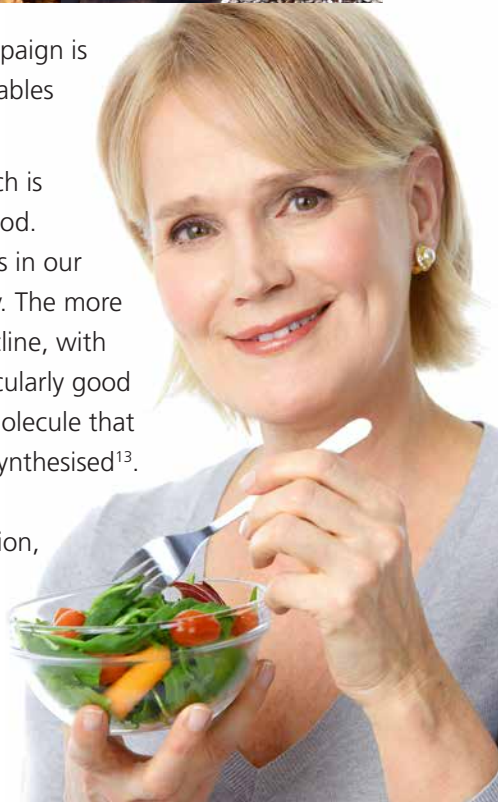
There are many studies showing how key nutrients like B vitamins, following a balanced diet, avoiding certain foods which can impair brain function, and adopting healthy lifestyle habits can help to optimise brain health, slowing or preventing degeneration. In a study by the University of Oxford[5], in a group of people with a diagnosis of Mild Cognitive Impairment (MCI), 50 percent were given a supplement of high-dose B vitamins (folate, B6 and B12) and the other half were given a placebo. In those with high homocysteine levels, the specific areas of the brain associated with Alzheimer's disease shrank eight times more slowly in those taking B vitamins than in those on the placebo. Furthermore, cognitive decline slowed in the B vitamin group. This is strongly indicative that the B vitamins may be substantially slowing, or even potentially arresting, the disease process in those with early stage cognitive decline. In addition to this, in a meta-analysis published in 2014 by BMC Public Health[6], homocysteine, which is effectively reduced by B vitamins, was considered one of the three strongest risk factors for the development of dementia, along with low education and decreased physical activity.

The most important B vitamins in supporting cognitive health are B6, B9 (folate) and B12. Foods such as poultry, leafy greens and seafood are rich in B6, which is essential for supporting new red blood cell growth, as well as playing an important role in brain metabolism as a cofactor in numerous enzyme reactions[7]. B9, also known as folate, can be found abundantly in vegetables such as spinach, broccoli and pulses, like beans and lentils. Folate is required for one-carbon transfer reactions, which are essential for the synthesis of DNA and RNA nucleotides, the metabolism of amino acids and the occurrence of methylation reactions[8], all of which contribute to brain health. Population-based studies have demonstrated a low folate status is associated with mild cognitive impairment, dementia (particularly Alzheimer's disease) and depression in healthy and neuropsychiatric diseased older individuals[9]. Finally, B12 is found in poultry, seafood, red meat and dairy products, but can also be found in fortified plant-based products such as soy milk and cereals. This is perhaps the most commonly deficient nutrient amongst the elderly, as efficiency in absorption and assimilation of B12 decreases in old age due to digestive issues and the prevalence of antacid prescription medication, which can cause issues with absorption. As we get older, it is important to take B12 supplements to overcome this problem. B12 is a significant cofactor for enzymes that are involved in the synthesis of DNA, fatty acids, and myelin, a protective barrier for the nerves. As a result, a B12 deficiency can lead to red blood cell disorders and neurological symptoms, such as cognitive decline[10].

Other key nutrients have been shown to play a significant role in protecting brain health and preventing cognitive decline. Omega-3 fatty acids are one such example. These essential fatty acids are key components of cell membrane structures; in the brain, they play a part in supporting the efficiency of nerve conductivity between nerve cells, as well as allowing the transport of vital nutrients into the cells and waste material out. These are crucial components of diet and supplementation, as the body cannot synthesise enough eicosapentaenoic and docosahexaenoic acids (EPA and DHA). Clinical observation studies have related deficiency of omega-3 to impaired brain performance and disease[11]. In one study[12], omega-3 supplementation was shown to promote amyloid-β clearance from the brain by mediating the function of the glymphatic system, which is responsible for clearing waste from the brain's interstitial fluids. The amyloid-β plaque is the hallmark of Alzheimer's and is the target of many pharmaceutical trials, none of which have so far been conclusive in managing the build-up of plaque that leads to neuronal loss and inflammation. Supplementation of omega-3 can be therapeutic in improving brain health, and food sources include oily fish like salmon, mackerel, sardines and herring. Flaxseeds, walnuts, macadamias and chia seeds can also be good sources for vegans and vegetarians.

Supplementation of omega-3 can be therapeutic
in improving brain health, and food sources include

Another important step in the Take Positive Action on Alzheimer's campaign is increasing antioxidant intake—substances predominantly found in vegetables and fruits which help to protect body cells from damage.



Essentially, they're antidotes to oxidation—a natural body process which is also linked to exposure to pollutants, cigarette smoke and toxins from food. Antioxidants are also vital for supporting thousands of chemical reactions in our bodies such as synthesising hormones, immune cells and creating energy. The more vegetables and fruit in a person's diet, the lower the risk of cognitive decline, with vegetables particularly protective. Eating a diet rich in vegetables is particularly good for supporting the body's own inbuilt antioxidant called glutathione, a molecule that may play a role in the development of Alzheimer's when not enough is synthesised[13]. Glutathione's role in the body is multifactorial; it helps to regulate and regenerate immune cells, as well as playing a vital role in cellular respiration, detoxification and providing defence against oxidative stress. It is a coenzyme which plays a role in various enzymatic reactions and contains sulphur chemical groups, which act as traps for free radicals and toxins, carrying them into bile and into the stool to be excreted from the body. When talking about glutathione in relation to the brain, it is important to note that the brain is especially sensitive to

oxidative damage, partly because it requires a large amount of oxygen to function normally, which leads to a high level of free radical production. Hence, antioxidant status is vital in mental health and neurological conditions.

There are many factors which can contribute to a deficiency in glutathione, diminishing defences against toxins and oxidative stress. Research shows poor diets high in refined sugars, processed foods and vegetable oils, and low in antioxidants and essential nutrients—as well as other factors like exposure to pollutants, stress, frequent infections and a high intake of medications—can all negatively impact glutathione levels[14]. Glutathione is made by a process requiring vitamin B6, which is normally recycled and continuously reused in the body. But when toxic load becomes heavier than is manageable, this process can become depleted.

To optimise glutathione levels, one can turn to diet and supplementation. A family of vegetables has been indicated to be particularly helpful in encouraging optimal levels of glutathione: cruciferous vegetables, which contain high levels of sulphoraphane, a phytochemical that encourages the production of glutathione. Vegetables such as broccoli, cabbage, kale, cauliflower, Brussels sprouts, kohlrabi, bok choy, turnips, watercress and rocket are all part of the cruciferous family. In addition, increasing selenium intake is a key factor in improving glutathione status. A co-factor of the antioxidant enzyme glutathione peroxidase, intake of this mineral is commonly low in the typical Western diet, which is deficient in the richest sources of selenium such as good quality organ meats, seafood and nuts such as Brazil nuts. Selenium depletion in farmed soils where vegetables are grown and animals pasture can also play a factor in this.

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Brain Health Product Development

by F.J. Roman, J. Meunier, V. Villard

Product development requires research and development, and when evaluating the effects of nutraceuticals on brain health and elucidating the underlying mechanisms involved, there are new testing models and techniques available. Amylgen has been working with various pharma and biotech companies interested in testing their compounds and ingredients for Alzheimer's disease (AD). There are many services to test nutraceuticals, probiotics and prebiotics for brain health.

Animal Models

New models have been developed to reproduce the brain ageing process, and studies on sensescence-accelerated mice (SAM) are particularly recommended. Rodent models allow trials to reproduce mental deficits occuring during the ageing process. These models are based on the central injection of a neurotoxic product ($A\beta_{25-35}$ peptide) or the induction of ageing by treatment with D-Galactose, the use of naturally aged animals or SAM.

$A\beta_{25-35}$ Peptide Induced Neurotoxicity

In a non-transgenic model of AD, first described in 1996 by T. Maurice[1], neurotoxicity is induced in mice by the intracerebroventricular (ICV) injection of amyloid-β_{25-35} ($A\beta_{25-35}$) fragment in oligomeric form. The toxicity induced by this injection has been repeatedly shown to result seven days after in neuroinflammation and reactive gliosis[2,3], pro-apoptotic caspases activity[2], oxidative stress[4], endogenously produced amyloid protein deposition[2], tau hyper phosphorylation[2] reduction in the number of neurons measured in hippocampal pyramidal cell layers[1,5], loss of cholinergic neurons[6], and memory deficits[1-5,7-12]. It is widely used to detect the neuroprotective potential of new drugs and natural derivatives. Interestingly, the $A\beta_{25-35}$ injection results not only in an aggressive amyloid toxicity but also in accumulation of endogenous Aβ species and tau hyper phosphorylation, as observed in AD physiopathology[2,3,12,13].

Senescence Accelerated Mice

Concerning studies on ageing, senescence accelerated mice (SAM), an inbred mouse model, derived from the AKR/J strain are widely used. The P8 substrain (SAM-P8) of these mice has a markedly shortened life span when compared to the R1 substrain (SAM-R1), which also shows

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a slower ageing process. Parallel to their premature aging, SAM-P8 mice also exhibit increased neurological senescence, immunosenescence, and age-related hematopoietic deficits, which closely mimic typical human ageing characteristics. Mitochondrial dysfunction, oxidative stress, and increased somatic DNA mutation rate all appear to be involved in the mechanisms responsible for the accelerated ageing process. For some authors, the SAM model represents the best model of sporadic AD available. This mouse system, with its homogeneous genetic background, provides an excellent experimental model for studying ageing and evaluating anti-ageing therapeutics as well as preventive treatments of AD.

D-Galactose induced toxicity

Another model proposed for more rapid testing is the D-galactose (DG) induced ageing mouse model. In rats and mice chronically treated with DG, a reducing sugar oxidative stress generator leads to the acceleration of senescence, which is very similar to the natural ageing in animals, such as a shortened lifespan. The animals show cognitive dysfunction, neurologic impairment associated with the increases of brain oxidative stress and the decreases of antioxidant enzyme activity, cholinergic degeneration, impairment of synaptic plasticity and neurogenesis, altered expression of amyloid-beta metabolism-associated molecules, reactive gliosis and neuroinflammation.

Maternal stress induced learning deficits in infants

A final model is using young rats or mice to test a product's effects on learning capacity in normal animals and in animals with a learning deficit produced by prenatal stress in the mother. In this model, pregnant rats are submitted to daily stress during the week before delivery. Infants display deficits of learning and memory similar to those seen in attention deficit hyperactivity disorder (ADHD). Evaluation of products is performed by inclusion in the diet during the first month following weaning.

Behaviour Tests

A series of behaviour tests have been designed to explore the various aspects of brain health during ageing. The most frequent complaint related to advancing in age is a decrease of intellectual performance concerning attention capacity, focus, flexibility, speed, creativity and memory. Further memory tests allow the exploration and analysis of many aspects of memory such as working memory, short-term and long-term memory, spatial and contextual processes, recognition, episodic and positively and negatively reinforced memory. These tests include: Y-maze/T-maze spontaneous alternation, step-through/step-down passive avoidance, place

learning in the water-maze, three panel runway task, water-maze active avoidance, water-finding test, fear conditioning, and novel object recognition. Alongside these memory tests are others evaluating depression and anxiety; two mood disorders which are very often linked to, or responsible for, memory troubles.

Associated Analyses

Animals tested for behavior are also characterised using biochemical, neurochemical and histological approaches. The treatment's efficacy can be evaluated by observing the many parameters translating the health status of an ageing brain—such as oxidative stress—by measuring lipid peroxidation, mitochondrial function (cytochrome C) and synaptic function (synaptophysin, GAP43, PSD95). Cholinergic system integrity, which is representative of cognitive performance, is assessed by measuring tissular levels of Acethylcholine (Ach), the labeling of Ach neurons in the nucleus basalis of Meynert and cholinergic projections in the hippocampus. Neuroinflammation is also related to brain ageing and these aspects can be studied using astroglial labelling with GFAP and microglial labeling with Iba1. Very interesting results are often achieved in studies on cellular cycle (CDK5, cyclin D1), neurogenesis capacity by immunolabeling of newly formed neurons (NeuN) and mature neurons (doublecortin, DCx) after bromodeoxyuridine (BrdU) injection, and BrdU immunohistochemistry. Finally, growth factors (NGF, BDNF) tissular levels are clear indicators of brain health.

Example Studies

The $A\beta_{25\text{-}35}$ model has been used to provide evidence of the important role of SV2B in AD14. This model demonstrated the activity of donepezil, one of the few compounds used in humans, but also ibuprofen[15], a γ-secretase inhibitor BMS299,897[16], a DYRK1A inhibitor Leucittine L41[17], synthetic neurosteroids - ent-pregnenolone sulphate/ ent-DHEA[18] or sigma 1 receptor agonists -Anavex 2-73[11] that are currently evaluated in clinical studies.

The effect of Biosfeen® a natural occurring compound extracted by Bioiberica, was presented at the 2017 AD/PD meeting in Vienna. The beneficial effect in terms of behavioral and biochemical aspects was characterised in two mouse models: the oligomeric $A\beta_{25\text{-}35}$ peptide-induced Alzheimer's disease and the SAM model with a sporadic development of the pathology. Animals were fed with Biosfeen included in the food pellets. After 14 days of treatment, animals were submitted to the intracerebro-ventricular (ICV) injection of $A\beta_{25\text{-}35}$ peptide and tested for different parameters, such as spatial working and contextual long-term

memories, inflammatory processes with IL1β, IL6 and TNFa, amyloid processing with C99 and $A\beta_{1-42}$, apoptosis by c-PARP, and Bax/Bcl2 ratio, and synaptic loss by PSD95 and synaptophysin, by ELISA assays. Oxidative stress was measured by lipid peroxidation measurement. Memory performance was evaluated every two months and markers of inflammation, apoptosis, synaptic alteration, oxidative stress, vascular alteration, amyloid processing and tau protein phosphorylation were measured at month 10. Biosfeen supplementation was shown to reverse memory deficits induced by the ICV injection of $A\beta_{25-35}$ peptide. In both models, the treatment was able to inhibit the induction of interleukins, the increase of $A\beta_{1-42}$, and C99 fragment, the induction of c-PARP and Bax, and the decrease of synaptophysin and PSD95. In SAM-P8 mice, VCAM increase and hyper phosphorylation of tau protein were also normalised. The neuroprotective effect of Biosfeen demonstrated in the acute model of $A\beta_{25-35}$ injection was verified in SAM-P8 mice developing AD along their lifetime.

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Takeaways for Your Business

Most people's traditional assumption is that cognitive health concerns are reserved for the elderly. It has always been a challenge to engage consumers to understand the role of targeted products in maintaining and preserving brain health and cognitive function as part of a healthy lifestyle.

Cognitive impairment is becoming a major health and social issue across nations as the global population ages. There are an estimated 46.8 million people worldwide living with dementia and this number has been predicted to double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. There are many studies showing how key nutrients like B vitamins, following a balanced diet, avoiding certain foods that can impair brain function, and adopting healthy lifestyle habits can help to optimise brain health, slowing or preventing degeneration.

Other key nutrients have been shown to play a significant role in protecting brain health and preventing cognitive decline, including omega-3 fatty acids and glutathione. Omega-3 supplementation has been shown to promote amyloid-β clearance from the brain by mediating the function of the glymphatic system. The amyloid-β plaque is the hallmark of Alzheimer's disease and is the target of many pharmaceutical trials, none of which have so far been conclusive in managing the build-up of plaque that leads to neuronal loss and inflammation.

There are many testing models and techniques available to companies interested in testing their compounds and ingredients for Alzheimer's disease. Rodent models allow trials to reproduce mental deficits occurring during the ageing process, often based on the central injection of amyloid-$\beta_{25\text{-}35}$. A series of behaviour tests have also been designed to explore the various aspects of brain health during ageing—the most frequent complaint related to advancing in age is a decrease of intellectual performance concerning attention capacity, focus, flexibility, speed, creativity and memory. Further tests allow the exploration and analysis of many aspects of memory such as working memory, short-term and long-term memory, spatial and contextual processes, recognition, episodic and positively and negatively reinforced memory.

Cognitive health is increasingly being considered and marketed as a long-term nutritional investment. While many natural ingredients can help manage the symptoms of severe neurological disorders, there is no magic pill solution—thus preventative measures are vital to lifelong cognitive health. Modern consumers know cognitive health is a vital component of good health throughout their lifetime—evolving research, a growing population at risk of neurodegenerative diseases, and consumers' desire for prevention at an earlier age will continue to advance the brain health sector. ●

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Next-Gen Ingredients for Brain Health

Wednesday, September 27 | 2-4pm

Nutritional ingredients for brain health have been touted for years, but what's on the frontier in terms of new applications for ingredients in the cognitive arena? During this Panel Discussion at SupplySide West, researchers share their insights on studies suggesting the benefits of omega-3s for neuroprotection, probiotics to bolster emotional IQ via the gut-brain axis, carotenoids that bolster cognitive performance, and adaptogens that can impact executive function and stress management.

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