



NUTRITION AND NEUROGENESIS

Romain Meeusen, PhD | Department of Human Physiology | Vrije Universiteit Brussel | Belgium

KEY POINTS

- Exercise and nutrition can influence brain development.
- Exercise and nutrition can slow down and reverse cognitive decline in the elderly.
- Exercise and nutrition influence brain health through several mechanisms to stimulate nerve cell generation or neurogenesis.
- Polyphenols have the potential to stimulate neurogenesis.
- Polyphenols improve memory, learning and general cognitive ability.
- Fruits, berries and vegetables are rich in antioxidants and bioactive compounds that may reduce disease risk stemming from reactive oxygen species and are also associated with cognitive benefits.

INTRODUCTION

Nutrition has a specific role in providing energy and building material for the body. The ability of nutrients to prevent and protect against diseases is starting to be recognized. Physical activity has also been associated with the reduction of a number of physical and mental disorders. Therefore, both nutrition and exercise are used as interventions to stimulate health. Recent data indicates that not only general health, but also brain functioning is influenced through exercise and nutritional interventions (Gomez-Pinilla, 2011). This Sports Science Exchange will describe how exercise and nutrition can influence neurogenesis or the generation of new nerve cells, and therefore have a neuroprotective effect.

NEUROGENESIS AND NEUROPLASTICITY

Neurogenesis is the process of generating new nerve cells, including neurons, astrocytes, glia and others. Neuroplasticity refers to the ability of the brain and the central nervous system (CNS) to adapt to environmental change, respond to injury and to acquire novel information by modifying neural connectivity and function. Neurotrophins are molecules that support neuroplasticity and in particular, are capable of signaling neurons to survive, differentiate or grow (Knaepen et al., 2010). Therefore, neurotrophins have gained increasing attention in research for the treatment and prevention of neurodegenerative and, more recently, metabolic diseases. Neurotrophic factors not only play a role in neurobiology, but also in central and peripheral energy metabolism. Their effect on synaptic plasticity in the CNS involves elements of cellular energy metabolism, and in the periphery, they take part in metabolic processes such as

enhancing skeletal muscle lipid oxidation via activation of adenosine monophosphate-activated protein kinase (AMPK). Neuroplasticity is an “activity-dependent” process and therefore nutrition and physical activity (exercise and training) appear to be key interventions that trigger the processes through which neurotrophins mediate energy metabolism and in turn neuroplasticity (Knaepen et al., 2010). Of all the neurotrophins, brain-derived neurotrophic factor (BDNF) seems to be the most sensitive to regulation by exercise and physical activity.

THE IMPORTANCE OF BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF)

BDNF is most abundant in brain areas that are associated with cognitive and metabolic regulation: the hippocampus and the hypothalamus. Hypothalamic BDNF appears to inhibit food intake and increase energy expenditure, leading to a negative energy balance. In the hippocampus, the involvement of BDNF in neural plasticity and neurogenesis is important to learning and memory. BDNF stimulates the development and differentiation of new neurons and promotes long-term potentiation (LTP), which is widely considered to be one of the major mechanisms underlying memory acquisition, consolidation and storage in the brain. It is also known to be controlled at the molecular level by the activation of a number of neuronal signaling pathways.

It is generally accepted that BDNF has a wide repertoire of neurotrophic and neuroprotective properties in the CNS and the periphery; namely, neuronal protection and survival, neurite expression, axonal and dendritic growth and remodelling, neuronal differentiation and synaptic plasticity and synaptic transmission efficacy (Cotman &

Berchtold, 2002). BDNF also plays a role in energy homeostasis, as BDNF deficiency is associated with increased weight gain in mice and humans, and hypothalamic BDNF administration can reduce food intake and increase energy expenditure, leading to lighter animals (Noble et al., 2011). Animal studies also revealed a neuroendocrine and/or metabotropic capacity of BDNF in the periphery, as BDNF is reported to lower blood glucose levels and increase insulin sensitivity (Knaepen et al., 2010). BDNF appears to affect metabolism and synaptic plasticity via insulin-like growth factor 1 (IGF1), which is synthesized in the liver, skeletal muscle and the brain (brain IGF1 receptors are expressed mainly in the hippocampus). A reduction of IGF1 signaling in rodents resulted in hyperglycemia and insulin resistance, and infusion of IGF1 into the brain decreased plasma insulin levels and increased insulin sensitivity. IGF1 also supports nerve growth and differentiation, neurotransmitter synthesis and release, and synaptic plasticity (Gomez-Pinilla et al., 2008). Exercise enhances hippocampal neurogenesis, most likely by stimulating the systemic production of IGF1. Importantly, IGF1 is also crucial for exercise-induced angiogenesis in the brain and may mediate the effects of BDNF via upstream gene mediation (Lista & Sorrentino, 2010).

BDNF and nutrition are also closely linked. Molteni et al. (2004) found that a high-fat diet in animals reduced hippocampal levels of BDNF, but that exercise was able to reverse this dietary decrease. Komori et al. (2006) showed a central interaction between the adipocyte-derived hormone leptin (which plays a key role in regulating appetite and energy metabolism) and BDNF expression in the hypothalamus of mice. Araya et al. (2008) reported that serum BDNF was increased in insulin resistant, overweight and obese subjects after a reduced-calorie diet. These findings confirm that BDNF is not only essential in the brain, but is also intimately connected with central and peripheral molecular processes of energy metabolism and homeostasis.

In search of mechanisms underlying plasticity and brain health, exercise and nutrition are known to induce a cascade of molecular and cellular processes that support brain plasticity. BDNF could play a crucial role in these mechanisms as animal and human studies have shown that exercise and/or training influences BDNF concentration (Gold et al., 2003; Radak et al., 2006; Van Praag, 2009; and Knaepen et al., 2010 for review). Advances in molecular biology have revealed the ability of food-derived signals to influence energy metabolism and synaptic plasticity and thus, mediate the effects of food on cognitive function, which is likely to have been crucial for the evolution of the modern brain (Gomez-Pinilla, 2008). Nutrition will influence both the development and health of brain structure and function, as it provides essential elements for the brain to create and maintain connections, which is critical for improved cognition.

NUTRITION AND COGNITION

The brain is a very metabolically active organ accounting for a high percentage of the total resting metabolic rate. As well as affecting the architecture of the brain, nutrition can also potentially influence

functioning from moment to moment (Benton, 2008). Non-invasive imaging techniques have clearly demonstrated that simply thinking about food can modulate neural activity in specific brain areas known to be involved in the cognitive control of appetitive behaviors, and can lead to physiological responses such as saliva, gastric acid and insulin secretion (Berthoud, 2007).

The brain is highly susceptible to oxidative damage because of the high metabolic rate and abundance of oxidizable material, such as the poly-unsaturated fatty acids that are prevalent in the plasma membranes of neural cells. Fruits and vegetables are among the most nutritious and healthy of foods, and are linked to the prevention of many chronic diseases. Plant foods are extremely complex and in spite of extensive efforts to identify their composition, the exact structures of the majority of nutrient compounds are not precisely known. However, it is acknowledged that fruits and vegetables are rich in antioxidants and bioactive compounds that may reduce disease risk stemming from reactive oxygen species which in turn are also associated with cognitive benefits. Based on animal models it has been suggested that fruit and vegetable supplements high in antioxidant activity may maximize neuronal and cognitive functioning in old age (Nurk et al., 2010). Several “antioxidant diets” have become popular for their positive effects on neural function. Berries, for example, have been shown to have strong antioxidant capacity. However, it is not clear how berry extracts benefit plasticity and cognition, but their effects may be associated with the maintenance of metabolic homeostasis, as this would protect membranes from lipid peroxidation and affect synaptic plasticity (Gomez-Pinilla, 2008).

A number of recent epidemiological and experimental studies have suggested that polyphenols have beneficial effects on brain health. Polyphenols are abundant micronutrients in plant-derived foods and are powerful antioxidants. Fruits and beverages such as tea, red wine, cocoa and coffee are major dietary sources of polyphenols. A significant inverse relationship between dementia or cognitive performance and the intake of polyphenols has been reported (Vauzour et al., 2010). In rats, polyphenols have been shown to increase hippocampal plasticity and improve learning and memory performance. Polyphenols have been reported to exert their neuroprotective actions through their potential to protect neurons against injury induced by neurotoxins, the ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function (Shukitt-Hale et al., 2008). Despite significant advances in our understanding of the biology of polyphenols, they are still mistakenly regarded as simply acting as antioxidants. However, recent evidence suggests that their beneficial effects involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling, and increased expression of genes that encode antioxidant enzymes, neurotrophic factors and protective proteins (Vauzour, 2012).

POLYPHENOLS AND THE BRAIN

The largest group of polyphenols is the flavonoids (Table 1). There

are six dietary groups of flavonoids: (1) flavones (e.g., apigenin, luteolin), which are found in parsley and celery; (2) flavanones/flavanonols (e.g., hesperetin, naringenin/astilbin, engeletin), which are mainly found in citrus fruit, herbs (oregano) and wine; (3) isoflavones (e.g., daidzein, genistein), which are mainly found in soy and soy products; (4) flavonols (e.g., kaempferol, quercetin), which are found in onions, leeks and broccoli; (5) flavanols (e.g., (+)-catechin, (-)-epicatechin, epigallocatechin and epigallocatechin gallate (EGCG), which are abundant in green tea, red wine and chocolate; and (6) anthocyanidins (e.g., pelargonidin, cyanidin, and malvidin), found in red wine and berry fruits.

The non-flavonoid group of polyphenols may be separated into two different classes: (1) the phenolic acids, including the hydroxybenzoic acids (HBAs; C1–C3 skeleton) and hydroxycinnamic acids (HCAs; C3–C6 skeleton); and (2) the stilbenes (C6–C2–C6 skeleton). Caffeic acid is generally the most abundant phenolic acid and is mainly found as the quinic ester, chlorogenic acid, in blueberries, kiwis, plums and apples. Resveratrol, the main stilbene, can be found in the cis or trans configurations, either glucosylated (piceid) or in lower concentrations as the parent molecule of a family of polymers such as viniferins, pallidol or ampelopsin A. The major dietary sources of resveratrol include grapes, wine and peanuts (Vauzour, 2012).

Flavonoids may act to protect the brain in a number of ways, including by protection of vulnerable neurons, the enhancement of existing neuronal function, or by stimulating neuronal regeneration (Vauzour et al., 2010). For example, flavonoids have been shown to protect neurons against oxidative stress and beta-amyloid-induced neuronal injury, and polyphenol-rich Ginkgo biloba extracts have been shown to protect hippocampal neurons from nitric oxide- and beta-amyloid-induced neurotoxicity (Luo et al., 2002). There is also growing interest in the potential of flavonoids to improve memory, learning and general cognitive ability. Human investigations have suggested that fruits and vegetables may have an impact on memory (Macready et al., 2009) and depression (How et al., 2007) and there is a large body of animal behavioral evidence to suggest that berries, in particular blueberries and strawberries, are effective at reversing age-related deficits in memory, improving object recognition memory, and modulating inhibitory fear conditioning (Joseph et al., 1998). The beneficial effects of flavonoid-rich foods and beverages on psychomotor activity in older animals have also been reported (Joseph et al., 1998). In addition to berries, tea, pomegranate, Ginkgo biloba and pure flavonols such as quercetin, rutin and fisetin have also been shown to be beneficial in reversing neuronal and behavioral aging. Furthermore, Ginkgo biloba has been shown to promote inhibitory avoidance conditioning in rats with high-dose intake leading to short-term, but not long-term, passive avoidance learning in senescent mice (Stoll et al., 1996).

The flavanol (-)-epicatechin, especially in combination with exercise, has been observed to enhance the retention of rat spatial memory in a water maze test. This improvement in spatial memory was shown to be associated with increased angiogenesis and neuronal spine density in the dentate gyrus of the hippocampus and with the up-regulation of genes associated with learning in the hippocampus (Stangl & Thuret, 2009). There is also extensive evidence that berries, in particular blueberries, are effective at reversing age-related deficits in motor function and spatial working memory (Rendeiro et al., 2009). For example, the latency period for rats to find a platform and the distance swum to a platform in the Morris water maze task was significantly reduced following blueberry supplementation. Such results may suggest favorable effects of the blueberry diet on locomotor activity in old animals. However, reductions in the time taken to make a choice may also reflect an improved memory component, where rats “remember” more rapidly and thus respond more quickly.

Polyphenols have been associated with a reduced risk of developing dementia, an improved cognitive performance in normal aging, and an improved cognitive evolution (Vauzour, 2012). Letenneur et al. (2007) performed a prospective cohort study over a 10-yr period among subjects aged 65 yr or older to investigate the relation among antioxidants, cognitive decline and dementia. A total of 1,640 subjects free from dementia at baseline and with reliable dietary assessment were re-examined four times over a 10-yr period. Cognitive functioning was assessed with three psychometric tests

Flavonoids

Group	Name(s)	Found In...
Flavones	Apigenin, luteolin	Parsley, celery
Flavanones/flavanonols	Hesperetin, naringenin, engeletin	Citrus fruits, oregano, wine
Isoflavones	Daidzein, genistein	Soy, soy products
Flavonols	Kaempferol, quercetin	Onions, leeks, broccoli
Flavanols	(+)-catechin, epicatechin, epigallocatechin, epigallocatechin gallate (EGCG)	Green tea, red wine, chocolate
Anthocyanidins	Pergaloidin, cyanidin	Red wine, berry fruits

Non-Flavonoids

Group	Name(s)	Found In...
Phenolic acids	Caffeic acid (Hydrobenzoic acids, hydroxycinnamic acids)	Blueberries, kiwis, plums, apples
Stilbenes	Resveratrol (viniferins, pallidol)	Grapes, wine, peanuts

Table 1: Polyphenols

and information on flavonoid intake was collected at baseline. After adjustment for age, sex and educational level, flavonoid intake was associated with better cognitive performance at baseline and with a better evolution of the performance over time. Subjects included in the two highest quartiles of flavonoid intake had better cognitive evolution than did subjects in the lowest quartile. After a 10-yr follow-up, subjects with the lowest flavonoid intake had significantly worse performance on psychometric tests, even after adjustment for several other potential confounders. In a related cross-sectional study, Nurk et al. (2009) examined the relation between the intake of three common foodstuffs that contain flavonoids (chocolate, wine and tea) and cognitive performance. Participants (2031, 70–74 yr, 55% women) recruited from the population-based Hordaland Health Study in Norway underwent cognitive testing. Participants who consumed chocolate, wine or tea had significantly better mean test scores and lower prevalence of poor cognitive performance than those who did not. Participants who consumed all three studied items had the best test scores and the lowest risks for poor test performance. The associations between intake of these foods and cognition were dose dependent, with a maximum effect at intakes of 10 g/d for chocolate and 75–100 mL/d for wine, and approximately linear for tea. Most cognitive functions were influenced by intake of these three foodstuffs. The effect was most pronounced for wine and modestly weaker for chocolate intake. Thus, in the elderly, a diet high in some flavonoid-rich foods was associated with better performance in several cognitive abilities in a dose-dependent manner.

MECHANISMS

The neuroprotective actions of dietary polyphenols and therefore flavonoids involve a number of effects within the brain, including a potential to protect neurons against injury induced by neurotoxins, the ability to suppress neuroinflammation, and the potential to promote memory, learning and cognitive function. While many of the mechanisms underpinning their beneficial effects remain to be elucidated, it has become clear that they in part involve decreases in oxidative/inflammatory stress signaling, increases in protective signaling, and may also involve protecting neurons against oxidative and inflammatory stressors.

The effects of polyphenols on cognition and against neurodegenerative processes appear to be mediated via their interactions with neuronal and glial signaling pathways that affect gene expression and interfere with the cell death mechanisms (Vauzour et al., 2010). Thus, dietary phytochemicals, in particular flavonoids, may exert beneficial effects in the CNS by protecting neurons against stress induced injury, by suppressing the activation of microglia and astrocytes, which mediate neuroinflammation, and by promoting synaptic plasticity, memory and cognitive function. Evidence supports the localization of flavonoids within the brain and thus these phytochemicals may be regarded as potential neuroprotective, neuromodulatory or anti-neuroinflammatory agents. It appears highly likely that such beneficial properties are

mediated by their abilities to interact with both protein and lipid kinase signaling cascades, rather than via their potential to act as antioxidants (Spencer, 2008).

The precise cellular sites of flavonoid actions are still unknown. Several possible pathways and action sites have been identified, but it is not known if flavonoid action requires cellular uptake or whether they are capable of mediating effects via extracellular receptor binding. Presently, there is no certainty either way, although flavonoid glucuronides, which are unable to enter cells to any significant degree, do not cause cellular effects (Vauzour, 2012). This suggests a requirement for cytosolic localization, although it could equally signify that the conjugation of flavonoids with glucuronide or sulphate moieties blocks receptor binding and therefore their cellular activity.

The concentrations of flavonoids encountered *in vivo* are sufficiently high to exert pharmacological activity at receptor, kinase and transcription factor sites. While precise sites of action are presently unknown, it is likely that their activity depends on their ability to: (1) bind to ATP sites on enzymes and receptors; (2) modulate the activity of kinases directly; (3) affect the function of important phosphatases, which act in opposition to kinases; (4) preserve Ca²⁺ homeostasis and prevent Ca²⁺-dependent activation of kinases in neurons; and (5) modulate signaling cascades downstream of kinases, *i.e.*, transcription factor activation and binding to promoter sequences.

The challenge now is to determine the precise site(s) of action of flavonoids within the signaling pathways and the sequence of events that allow them to regulate neuronal function in the CNS (Spencer, 2008, Spencer et al., 2012). Signaling pathways induced by polyphenols may be positive in the treatment of proliferative diseases, but they could be detrimental to the nervous system, at least at high concentrations, where these same pathways act to control neuronal survival and synaptic plasticity. Thus, flavonoid interactions with intracellular signaling pathways could have unpredictable outcomes and will be dependent on the cell type (*i.e.*, neurons, astrocytes, etc.), the disease studied, and the stimulus applied. In summary, it is evident that flavonoids are potent bioactive molecules and a clear understanding of their mechanisms of action as modulators of cell signaling will be crucial in the evaluation of their potential to act as inhibitors of neurodegeneration or as modulators of brain function (Spencer, 2008; Vauzour et al., 2010).

PRACTICAL APPLICATIONS AND CONCLUSIONS

Exercise and nutrition are both powerful stimuli to influence the brain. The exploration of brain function is in its infancy, but it is clear that physical activity and nutrition have health-enhancing effects on the brain. There is a growing interest in the potential of polyphenols to improve memory, learning and general cognitive ability. It is evident that flavonoids (most common form of polyphenols) are potent bioactive molecules and a clear understanding of their mechanisms of action as modulators of cell signaling will be crucial in the

evaluation of their potential to act as inhibitors of neurodegeneration, or as modulators of brain function. While the balance of evidence suggests that polyphenol effects contribute to the benefits of a high intake of fruits and vegetables, the extent of the contribution *in vivo*, and at physiological relevant concentrations, remains uncertain. More research is required to prove whether this class of compounds is most likely to result in health benefits and to determine potential beneficial effects in slowly developing neurodegenerative disorders. In view of the varied biological activities, the consumption of polyphenol-rich foods throughout life holds the potential to limit neurodegeneration and to prevent or reverse age-dependent deteriorations in cognitive performance.

REFERENCES

- Araya, A.V., X. Orellana, and J. Espinoza (2008). Evaluation of the effect of caloric restriction on serum BDNF in overweight and obese subjects: preliminary evidences. *Endocrine* 33: 300-304.
- Benton, D. (2008). The influence of children's diet on their cognition and behavior. *Eur. J. Nutr.* 47: 25-37.
- Berthoud, H.R. (2007). Interactions between the "cognitive" and "metabolic" brain in the control of food intake. *Physiol. Behav.* 91:486-498.
- Cotman, C., and N. Berchtold (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends Neurosci.* 25: 295-301.
- Gold, S.M., K. Schulz, S. Hartmann, M. Mladek, U.E. Lang, R. Hellweg, R. Reer R, K.M. Braumann, and C. Heesen (2003). Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *J. Neuroimmun.* 183:99-105.
- Gomez-Pinilla, F. (2008). Brain foods: the effects of nutrients on brain function. *Nat. Rev. Neurosci.* 9: 568-578.
- Gomez-Pinilla, F., S. Vanyman, and Z. Ying (2008) Brain-derived neurotrophic factor functions as a metabotrophin to mediate the effects of exercise on cognition. *Eur. J. Neurosci.* 28: 2278-2287.
- Gomez-Pinilla, F. (2011). The combined effects of exercise and foods in preventing neurological and cognitive disorders. *Prevent. Med.* 52 S75-S80.
- How, P., R. Cox, J. Ellis, and J. Spencer (2007). The impact of plant-derived flavonoids on mood, memory and motor skills in UK adults. *Proc. Nutr. Soc.* 66: 87A.
- Joseph, J., B. Shukitt-Hale, N. Denisova, R. Prior, G. Cao, A. Martin, G. Taghialatela, and P. Bickford (1998). Long-term dietary strawberry, spinach, or vitamin E supplementation retards the onset of age-related neuronal signal-transduction and cognitive behavioral deficits. *J. Neurosci.* 18: 8047-8055.
- Knaepen, K., M. Goekint, E. Heyman, and R. Meeusen (2010). Neuroplasticity: the effect of acute exercise and training on peripheral brain-derived neurotrophic factor; a systematic review of experimental studies in human subjects *Sports Med.* 40: 765-801.
- Komori, T., Y. Morikawa, K. Nanjo, and E. Senba (2006). Induction of brain-derived neurotrophic factor by leptin in the ventromedial hypothalamus. *Neuroscience* 139: 1107-1115.
- Letenneur, L., C. Proust-Lima, A. Le Gouge, J. Dartigues, and P. Barberger-Gateau (2007). Flavonoid intake and cognitive decline over a 10-year period. *Am. J. Epidemiol.* 165: 1364-1371.
- Lista, I., and G. Sorrentino (2010). Biological mechanisms of physical activity in preventing cognitive decline. *Cell. Mol. Neurobiol.* 30: 493-503.
- Luo, Y., J. Smith, V. Paramasivam, A. Burdick, K. Curry, J. Buford, I. Khan, W. Netzer, H. Xu, and P. Butko (2002). Inhibition of amyloid-beta aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. *Proc. Natl. Acad. Sci. USA* 99: 12197-12202.
- Macready, A., O. Kennedy, J. Ellis, C. Williams, J. Spencer, and L. Butler (2009). Flavonoids and cognitive function: A review of human randomized controlled trial studies and recommendations for future studies. *Genes Nutr.* 4: 227-242.
- Molteni, R., A. Wu, and S. Vaynman (2004). Exercise reverses the harmful effects of consumption of a high-fat diet on synaptic and behavioral plasticity associated to the action of brain-derived neurotrophic factor. *Neuroscience* 123: 429-440
- Noble, E., C. Billington, C. Kotz, and C. Wang (2011). The lighter side of BDNF. *Am. J. Physiol.* 300: R1053-R1069.
- Nurk, E., H. Refsum, C. Drevon, G. Tell, H. Nygaard, K. Engedal, and D. Smith (2009). Intake of flavonoid-rich wine, tea, and chocolate by elderly men and women is associated with better cognitive test performance. *J. Nutr.* 139: 120-127.
- Nurk, E., H. Refsum, C. Drevon, G. Tell, H. Nygaard, K. Engedal, and D. Smith (2010). Cognitive performance among the elderly in relation to the intake of plant foods. The Hordaland Health Study. *Br. J. Nutr.* 104: 1190-1201.
- Radak, Z., A. Toldy, Z. Szabo, S. Siamillis, C. Nyakas, G. Silye, J. Jakus, and S. Goto (2006). The effects of training and detraining on memory, neurotrophins and oxidative stress markers in rat brain. *Neurochem. Int.* 49: 387-392.
- Rendeiro, C., J. Spencer, D. Vauzour, L. Butler, J. Ellis, and C. Williams (2009). The impact of flavonoids on spatial memory in rodents: From behaviour to underlying hippocampal mechanisms. *Genes Nutr.* 4: 251-270.
- Shukitt-Hale, B., F.C. Lau, A.N. Carey, R.L. Galli, E.L. Spangler, D.K. Ingram, and J.A. Joseph (2008). Blueberry polyphenols attenuate kainic acid-induced decrements in cognition and alter inflammatory gene expression in rat hippocampus. *Nutr. Neurosci.* 11: 172-182.
- Spencer, J. (2008). Diet and mental health food for thought: the role of dietary flavonoids in enhancing human memory, learning and neuro-cognitive performance. *Proc. Nutr. Soc.* 67: 238-252.
- Spencer, J.P., K. Vafeiadou, R.J. Williams, and D. Vauzour (2012). Neuroinflammation: modulation by flavonoids and mechanisms of action. *Mol. Aspects Med.* 33: 83-97.
- Stangl, D., and S. Thuret (2009). Impact of diet on adult hippocampal neurogenesis. *Genes Nutr.* 4: 271-282.
- Stoll, S., K. Scheuer, O. Pohl, and W. Muller (1996). Ginkgo biloba extract (EGb 761) independently improves changes in passive avoidance learning and brain membrane fluidity in the aging mouse. *Pharmacopsychiatry* 29: 144-149.
- Van Praag, H. (2009). Exercise and the brain: something to chew on. *Trends Neurosci.* 32: 283-290.
- Vauzour, D. (2012). Dietary polyphenols as modulators of brain functions: biological actions and molecular mechanisms underpinning their beneficial effects. *Oxid. Med. Cell. Longev.* PMID: 22701758
- Vauzour, D., A. Rodriguez-Mateos, G. Corova, M. Oruna-Concha, and J. Spencer (2010). Polyphenols and human health: prevention of disease and mechanisms of action. *Nutrients* 2:1106-1131.