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Is there a role for diet in cognitive rehabilitation?

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Introduction

The body of knowledge linking diet and nutrition with incidence of chronic disease, health promotion and optimal physiological functioning is large and compelling. Until recently, however, this link had been recognized to apply only in the broadest sense to brain health and the support of cognitive function. In this chapter, both chronic diet, a person's usual pattern of eating and drinking, and acute diet, the consumption of a single food or meal, will be examined for their ability to influence those biological processes underlying the functional benefits associated with cognitive rehabilitation. Only inferences can be made; nevertheless, results from cellular, animal and population-based studies provide support for diet's ability to influence neuronal survival and growth, pathological neurodegeneration, and molecular and biochemical processes involved in neuronal communication and memory formation. To apply this information to rehabilitation, our underlying assumption is that for cognitive gain to occur, new neuronal networks must be established. To support these new networks, synaptogensis and potentially neurogenesis will be required and consequently diet- or health-induced processes that facilitate or enhance synaptic plasticity, the potential for neurogenesis, or overall neuronal health and metabolism will associate with superior rehabilitation outcome.

Thus the underlying hypotheses to be explored are that:

- Chronic diet, through its ability to modulate overall neuronal health, can facilitate or interfere with the establishment of new networks essential for cognitive gain.
- Acute diet, by providing essential substrates and energy to support neuronal metabolism, facilitates biochemical processes needed for memory formation occurring during rehabilitation training.

Role of chronic diet

This section explores evidence showing that:

- Consumption of poor quality diets, especially those high in fat and low in fruits, vegetables and cereals, interfere with numerous physiologic processes necessary to support memory formation, establishment of new neuronal networks and neuronal survival.
- This is mediated by disturbances in brain insulin signaling, enhancement of neuroinflammation, and increases in oxidative damage.
- By contrast, diets containing fatty fish, such as salmon, and fruits and vegetables, because of their high quality fat and antioxidant contents, protect the brain from the aforementioned events thereby allowing for a more conducive environment needed for physiologic responses to cognitive rehabilitation.

Numerous cross-sectional and prospective epidemiologic studies demonstrate associations between diet quality and retention of cognitive abilities with aging. In general, older individuals consuming diets high in fat and low in fruits, vegetables and cereals perform worse on cognitive tasks relative to

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age-matched individuals with better-quality diets even after adjustment for other lifestyle characteristics (Barberger-Gateau *et al.*, 2002; Luchsinger & Mayeux, 2004; Ortega *et al.*, 1997; Panza *et al.*, 2004). A variety of nutrients, including fat quality and content, antioxidants and vitamins such as folate and B12 are implicated. Both brain-specific mechanisms and the fact that inappropriate intake of these nutrients concomitantly elevate risk for chronic diseases, such as cardiovascular disease (CVD), hypertension (Newman *et al.*, 2005) and type 2 diabetes mellitus (T2DM) (Arvanitakis *et al.*, 2004; Luchsinger *et al.*, 2004; Ott *et al.*, 1999; Peila *et al.*, 2002), which are themselves independent risk factors for cognitive decline, likely explain their influence.

There is no question that diet is a major risk factor for cerebrovascular disorders, including stroke, due to its ability to modulate blood pressure and blood lipid levels. Nevertheless, given the known contribution of vascular disorders to dementia risk (Honig *et al.*, 2003), it will be assumed that screening and if warranted, medical management including diet change and medications, will have been implemented in those entering rehabilitation programs. Rather than concentrate on diet's recognized role in maintaining vascular health, we will argue that the presence of diet-induced insulin resistance (IR) or overt T2DM, because of their adverse brain effects particularly as they relate to impaired insulin signaling and its downstream consequences, have the potential to interfere with physiologic processes of rehabilitation and that if uncorrected, could be a major modifiable factor contributing to rehabilitation failure. By contrast, a healthy diet including fish, fruits and vegetables, is linked to preservation and/or protection against many adverse processes which need to be minimized to maintain neuronal health – a prerequisite to establishing new networks.

Neuropathologic events associated with disruptions to brain insulin, insulin-mediated cell signaling, inflammation and oxidative stress

It is increasingly recognized that disruptions in brain insulin mediated cell signaling, apparent in those with IR or T2DM, result in brain insults leading to cognitive decline and neuropathologic progression of Alzheimer's disease (AD) (Craft, 2005; Craft & Watson, 2004; Zhao & Alkon, 2001). This section will briefly review data demonstrating that:

- Insulin signaling is intimately involved in memory processing.
- Its disruption is associated with development of neuropathologic hallmarks of Alzheimer's disease, including accumulation of amyloid-beta peptide (Aβ) involved in plaque formation and production of hyperphosphorylated tau proteins involved in neurofibrillary tangle formation.
- Loss of insulin signaling can interfere with the action of other neurotrophins, and facilitate neuroinflammatory processes which collectively impede synaptic plasticity and contribute to neuronal death.
- Dietary components, especially dietary fat, can lead to loss of insulin signaling and promotion of inflammation which may contribute to less effective rehabilitation.

The importance of understanding the potential adverse consequences of IR and T2DM can not be understated. Given that half of all adults over 60 years of age have some degree of IR (Kahn *et al.*, 2005), it should be assumed that many in rehabilitation programs are experiencing these adverse events to varying degrees and that, if uncorrected, poorer outcome would be anticipated as injured and dying neurons would be unlikely to have the resources to establish new networks. This is compounded by the fact that the brain insult or injury leading to the need for rehabilitation likely involved neuronal death or dysfunction, thereby minimizing the protection normally afforded by redundancy.

Role of insulin signaling in memory processing

Evidence demonstrating the essentiality of brain insulin signaling for memory processing is compelling (see Table 16.1 for synopsis of this evidence). These effects are in addition to the more traditional role of insulin in stimulating cerebral glucose metabolism in specific brain areas versus total

Table 16.1. Evidence linking brain insulin signaling to memory processing.

Localization of the insulin receptor (IRc) to key brain regions including the frontal and cerebral cortices, hippocampus and medial temporal lobe	(Craft & Watson, 2004; Zhao *et al.*, 1999; Zhao & Alkon, 2001)
In situ brain insulin synthesis	(Devaskar *et al.*, 1994; Rulifson *et al.*, 2002; Schechter *et al.*, 1988)
Presence of the major signaling pathways including phosphotidylinositol-3 kinase (PI3K) and its downstream effector Akt and the cytoplasmic intermediate protein Shc and their convergence on mitogen-activated protein kinase (MAPK) activation	(Foulstone *et al.*, 1999; Orban *et al.*, 1999; Ryu *et al.*, 1999; Yang & Raizada, 1999; Zhao *et al.*, 1999)
Insulin and IRc stimulated synthesis of those proteins necessary and sufficient for long-term memory formation	(Alkon *et al.*, 2005; Kahn *et al.*, 1993; Zhao & Alkon, 2001)
Enhancement of insulin signaling pathways when animals are exposed to learning paradigms	(Bank *et al.*, 1988; Olds *et al.*, 1989; Zhao *et al.*, 1999)
Ability of insulin signaling to modulate long-term potentiation (LTP) – a molecular model of memory – by regulation of the pre- and postsynaptic synthesis and activity of neurotransmitters including acetylcholine, GABA, serotonin, dopamine and NMDA	(Devaskar *et al.*, 1994; Havrankova *et al.*, 1978; Zhao & Alkon, 2001)

brain glucose uptake – in this sense brain remains an insulin-insensitive organ. Overlapping distributions of insulin, insulin receptors (IRc), and insulin-sensitive glucose transporters in the hippocampus provide a platform for insulin-stimulated glucose uptake which is known to improve a wide range of memory functions (Craft & Watson, 2004; Korol & Gold, 1998). Consistent with this molecular role are studies indicating that acute insulin elevations facilitate memory function when given at optimal doses to rodents (Park *et al.*, 2000) and humans, provided there is adequate glucose availability (Craft *et al.*, 1999; Reger *et al.*, 2006).

Brain insulin signaling becomes increasingly impaired with IR and T2DM since chronic elevations in plasma insulin downregulate brain insulin transport and IRc expression, such that the brain experiences an insulin-deficient state (Baura *et al.*, 1996; Wallum *et al.*, 1987), placing individuals at increased risk for cognitive decline (Awad *et al.*, 2004). Indeed, cognitive deficits are already apparent in those with IR. For example, we report decrements in delayed verbal memory that associate with measures of IR (Kaplan *et al.*, 2000) and glycemic control (Greenwood *et al.*, 2003; Papanikoloau *et al.*, 2006), as well as impaired long-term memory and indication of disrupted brain insulin signaling in genetically obese and insulin-resistant Zucker rats (Winocur *et al.*, 2005). Many patients with AD show evidence of deficient brain insulin signaling, including lower cerebrospinal fluid (CSF) insulin levels, and resistance to insulin-mediated memory facilitation, compared with healthy controls (Craft *et al.*, 1998, 2003), and progressive loss of insulin and IRc expression accompanied by loss of downstream signaling through PI3K/Akt (Frolich *et al.*, 1998; Rivera *et al.*, 2005). Thus, progressive loss of brain insulin signaling occurs in tandem with cognitive decline throughout the spectrum of age-associated memory loss to AD, with many arguing a cause and effect relationship.

Loss of insulin signaling and neuropathologic events

While loss of insulin signaling in and of itself could interfere with rehabilitation success due to impaired memory processing, other pathologic events

associated with brain insulin deficiency could have more serious consequences as they relate to neuronal plasticity and survival. Specifically, brain insulin deficiency leads to increased brain accumulation of Aβ – accumulation of which is thought to be an initiating event in AD pathogenesis (Oddo *et al.*, 2003) – and neuronal death by a variety of mechanisms. Both decreases in brain insulin levels per se and disturbances in insulin-mediated cell signaling play a role as the former primarily impairs the brain's ability to degrade and export Aβ while the latter primarily increases its production. This accumulation, in turn, leads to disruptions in other aspects of cell signaling, including those involved in long-term potentiation (LTP). Loss of insulin-mediated cell signaling may also contribute to the formation of neurofibrillary tangles, another hallmark of AD highly correlated with cognitive deterioration (Arriagada *et al.*, 1992), since this signaling pathway suppresses enzymes involved in tau hyperphosphorylation (see Table 16.2 for synopsis of this evidence).

Table 16.2. Evidence linking negative and positive attributes of chronic diet to neuronal characteristics essential for successful neurorehabilitation.

Potential mechanisms for proposed adverse effect of a high-fat diet containing mostly saturated fatty acids and few servings of fruits or vegetables	
Promotion of insulin resistance and peripheral hyperinsulinemia which in turn can lead to:	
Decreased brain insulin, which in turn associates with brain Aβ accumulation by:	(Baura *et al.*, 1996; Wallum *et al.*, 1987)
Decreasing brain Aβ degradation	(Authier *et al.*, 1996; Craft & Watson, 2004; Farris *et al.*, 2003, 2004; Vekrellis *et al.*, 2000)
Impairing brain Aβ export	(Carro *et al.*, 2002; Gasparini & Xu, 2003; Nestler *et al.*, 1990; Stein & Johnson, 2002)
Decreased transport and expression of Aβ carrier proteins	(Carro *et al.*, 2002; Gasparini & Xu, 2003; Nestler *et al.*, 1990; Stein & Johnson, 2002)
Inhibited peripheral and brain Aβ degradation by insulin degrading enzyme	(Authier *et al.*, 1996; Craft & Watson, 2004; Farris *et al.*, 2003, 2004; Vekrellis *et al.*, 2000)
Loss of brain insulin mediated PI3K/Akt signaling also enhances Aβ accumulation by:	(Frolich *et al.*, 1998; Rivera *et al.*, 2005)
Increasing caspase-3 activity which	
Contributes to apoptotic cell death	(Yuan & Yankner, 2000)
Results in production of short cytoplasmic APP fragments which in turn may increase Aβ generation	(Dumanchin-Njock *et al.*, 2001; Galvan *et al.*, 2002; Gervais *et al.*, 1999; Lu *et al.*, 2000; Marin *et al.*, 2000; Su *et al.*, 2002; Tesco *et al.*, 2003; Uetsuki *et al.*, 1999)
Aβ accumulation then:	
Disrupts LTP and neurotransmission due to its cytotoxic properties	(Kar *et al.*, 2004; Oddo *et al.*, 2003)
Further enhance caspases allowing for escalation of Aβ accumulation	(Marin *et al.*, 2000; Uetsuki *et al.*, 1999)
Loss of brain insulin mediated PI3K/Akt signaling may also contribution to the formation of neurofibrillary tangles through:	(Hong & Lee, 1997; Schechter *et al.*, 2005a, 2005b)
Disinhibition of glycogen-synthase kinase-3	(Hong & Lee, 1997; Schechter *et al.*, 2005b)
Increased inflammation and oxidative stress	(Dimopoulos *et al.*, 2006; Fishel *et al.*, 2005)
Decreased neurotrophin levels and activity can lead to:	(Duan *et al.*, 2003; Yu *et al.*, 2006)

Table 16.2. (*cont.*)

Disrupted LTP, and decreased neuronal survival, and brain plasticity	(Mattson *et al.*, 2004)
Decreased neurogenesis and cell survival	(Yuan & Yankner, 2000)
Potential mechanisms for proposed beneficial effect of a low-fat diet enriched in omega-3 fatty acids that includes 10 servings of fruits or vegetables, and limits saturated fat intake	
Maintained or improved DHA levels and overall fatty acid profile	(Bourre, 2004)
Maintained or improved peripheral insulin levels and sensitivity, which in turn could protect against events described above	(Storlien *et al.*, 1987; Taouis *et al.*, 2002)
Stimulation and protection of insulin signaling including PI3K/Akt	(Akbar *et al.*, 2005; Joseph *et al.*, 2003; Mandel *et al.*, 2005; Taouis *et al.*, 2002; Weinreb *et al.*, 2004)
Inhibited Aβ production	(Lim *et al.*, 2001, 2005; Yang *et al.*, 2005)
Maintenance of synaptic plasticity	(Calderon & Kim, 2004; Calon *et al.*, 2004)
Increased neuroprotectin D1 leading to increased anti-apoptotic and neuroprotective, anti-inflammatory gene-expression programs	(Lukiw *et al.*, 2005; Marcheselli *et al.*, 2003)
Decreased inflammation and oxidative stress	(Cao *et al.*, 2005; Joseph *et al.*, 2005; Lau *et al.*, 2005; Lim *et al.*, 2001; Maher *et al.*, 2004; Yang *et al.*, 2005)
Maintained or improved neurotrophin levels and activity	(Casadesus *et al.*, 2004)
Maintained or improved neurogenesis and cell survival	(Calderon & Kim, 2004)

Insulin resistance, type 2 diabetes mellitus, inflammation and oxidative stress

Insulin resistance increases inflammatory responses and oxidative stress. Recent observational studies have implicated serum levels of pro-inflammatory cytokines with lower cognitive status, lower nerve conduction velocity and greater cognitive decline among senior citizens (Di Iorio *et al.*, 2006; Weaver *et al.*, 2002; Wright *et al.*, 2006), even after adjustments for a wide variety of socio-demographic variables. Low-grade, systemic inflammation, as often found in insulin-resistant individuals, is associated with decline and early cognitive deterioration (Dimopoulos *et al.*, 2006). Our own studies in adults with T2DM suggest that those individuals carrying a single nucleotide polymorphism (SNP) which reduces the expression of tumor necrosis factor-alpha have better delayed verbal memories and show less loss of its function over 48 weeks compared with those not carrying the SNP (Chui *et al.*, 2007). Indeed not only do individuals diagnosed with metabolic syndrome, a condition characterized by IR, exhibit greater cognitive impairment than healthy controls, but within the metabolic syndrome group, those participants with the greatest inflammation exhibited the greatest impairment (Yaffe *et al.*, 2004). The role of peripheral hyperinsulinemia to produce systemic inflammation is well known (Caballero, 2003), and can translate into increased markers of central nervous system (CNS) inflammation (Fishel *et al.*, 2005).

Interestingly, increased CNS inflammation was positively correlated with changes in Aβ suggesting that synchronous hyperinsulinemia-induced increases in Aβ and inflammation may represent an important pathway through which IR promotes both cognitive deterioration and AD pathology. This is compounded by the facts that Aβ cytotoxicity, through its pro-oxidant properties (Behl *et al.*, 1994), may feedback to promote further production (Misonou *et al.*, 2000) and that inflammatory cytokines downregulate brain expression of Aβ scavengers

possibly leading to increased deposition. Increased pro-inflammatory cytokine levels can downregulate PI3K/Akt in aged rat brains leading to subsequent caspase activation (Maher *et al.*, 2004) suggesting that insulin-related signaling is negatively affected by inflammation ultimately leading to increased neuronal death.

Insulin resistance and neurotrophins

The interplay between insulin levels and neurotrophins represents another way in which IR can negatively impact on brain function. Traditional neurotrophins, including brain-derived neurotrophic factor (BDNF), like insulin, use tyrosine kinase signal transduction to activate downstream targets including PI3K/Akt (Mattson *et al.*, 2004). Obese and typically insulin-resistant mice exhibit reduced BDNF levels (Duan *et al.*, 2003) which can adversely affect LTP, neuronal survival and brain plasticity, and consequently memory and learning (Mattson *et al.*, 2004). Conversely, treatment of neurons with BDNF promotes PI3K/Akt signaling, and reduces caspase activity, highlighting the possible importance of neurotrophins in the regulation of insulin signaling and vice-versa (Lesne *et al.*, 2005). Plasma hyperinsulinemia also downregulates the transport of insulin-like growth factor-1 (IGF-1) across the blood–brain barrier from the periphery where it is synthesized (Yu *et al.*, 2006). Although not a traditional neurotrophin, IGF-1 rapidly and significantly stimulates the process of membrane assembly at the axonal growth cone through direct stimulation of the PI3K/Akt pathway – an effect not shared with BDNF (Laurino *et al.*, 2005; Pfenninger *et al.*, 2003) and increases neurite sprouting and outgrowth (Aizenman & de Vellis, 1987; Caroni & Grandes, 1990). The high degree of amino acid homology between IGF-1 and insulin allows for cross-reactivity between their respective membrane receptors, making their signaling cascades almost indistinguishable (Dupont & LeRoith, 2001; Pandini *et al.*, 2002). Furthermore, like insulin, IGF-1 activity can be reduced by pro-inflammatory cytokines (Hansen *et al.*, 1999; Maher *et al.*, 2006). Thus, IR can negatively impact on the processes of neuronal growth, plasticity and survival through its ability to reduce brain levels of neurotrophins like IGF-1 and BDNF. Given recent findings that learning may be accompanied by hippocampal neurogenesis in adult rodent brains (Winocur *et al.*, 2006), and the reliance of neurogenesis on similar biologic signals, like IGF-1 and BDNF (Mattson *et al.*, 2004), this negative pathway has the potential to impair a number of processes recruited during learning and presumably rehabilitation ultimately leading to worse cognitive outcomes.

Diet as a contributor to insulin resistance

There is no question that most cases of IR are mediated by inappropriate lifestyle, including diet. Excess dietary fat, particularly saturated fat, worsens IR in humans while animal studies indicate that dietary saturated fat intake can actually induce IR (Riccardi *et al.*, 2004; Storlien *et al.*, 1991). Corroborating this assertion are our studies of high saturated fat feeding that consistently link both the level and type of fat to cognitive deficits in young adult rats. These deficits are widespread, influencing a number of cognitive domains, with hippocampally mediated memory functions being the most adversely affected (reviewed in Winocur & Greenwood, 2005). High fat feeding also contributes to AD pathology by inducing even higher levels of Aβ in Tg_{2576} mice (Ho *et al.*, 2004), and increasing brain inflammation and decreasing BDNF levels (Duan *et al.*, 2003; Molteni *et al.*, 2004; Zhang *et al.*, 2005).

Collectively, studies indicate that consumption of high-fat diets adversely influences many biological parameters including neuronal signaling cascades involved in memory, neurotransmission, neuronal growth and survival, AD pathology, and neurotrophin activity – either directly or through promotion of IR – ultimately leading to impairments in behavioral function. Importantly, in most instances, animal-based diets were modeled to provide dietary fat levels consistent with upper limits of typical North American diets and epidemiologic data demonstrate relationships between high-fat diets and

poorer cognitive function (Morris *et al.*, 2003a). Without assessing, and where necessary recommending dietary change, the continued consumption of a diet high in saturated fat would not be supportive, and perhaps even harmful, to neuronal processes required for successful cognitive rehabilitation. Importantly, clinical studies demonstrating improvements in cognitive function in adults with T2DM who improve their glycemic control by reducing saturated fat intake and consuming more dietary fibre (Gradman *et al.*, 1993; Meneilly *et al.*, 1993; Naor *et al.*, 1997; Ryan *et al.*, 2006) suggest that some of the adverse effects of diabetes are reversible, meaning that it is never "too late" to implement change.

The preceding discussion focused on negative effects of diet on brain integrity and function. By contrast, healthier diets lower the risk of developing IR or T2DM and help protect the brain from their deleterious effects. Indeed, there is especially compelling evidence that two nutrients – omega-3 fatty acids and plant-based antioxidants – are especially beneficial.

Omega-3 fatty acids and fish oils

The omega-3 (ω-3) family of fatty acids, especially those found in fish oils, have the capacity to modulate a wide variety of cellular processes through their ability to modulate membrane composition and function, suppress adverse inflammatory events and directly or indirectly modulate gene expression. This family of fatty acids is characterized by their relatively long chain length and large number of double bonds between carbons causing a U-shaped or "kinked" molecular conformation. In contrast, saturated fatty acids typically contain fewer carbon atoms, lack double bonds, and have a straight chain conformation. In this section we will briefly present evidence that:

- Omega-3 fatty acids are necessary dietary components that are highly enriched in nervous tissues and participate in a wide variety of functions including long-term potentiation, membrane function and neurotransmitter release.
- Reduced ω-3 fatty acid availability decreases levels in the brain and insulin signaling resulting in compromised cognitive function in aging animals and explaining strong epidemiological relationships in humans.
- Reduced dietary ω-3 fatty acids promotes AD-related neuropathology.
- Omega-3 fatty acids modulate production of neurotrophins and neuroinflammatory markers.

Although dietary ω-3 fatty acids appear protective against AD and cognitive decline in large, prospective studies, this effect is somewhat specific to docosahexaenoic acid (DHA) (Barberger-Gateau *et al.*, 2002; Morris *et al.*, 2003b, 2005). Docosahexaenoic acid is a long-chain (22 carbons, 6 double bonds) ω-3 fatty acid found in especially high amounts in fish oil. Intake changes even in late-life alter brain fatty acid profiles and behavioral outcomes (Bourre, 2004; Winocur & Greenwood, 2005). Historically, it is thought humans evolved consuming a diet containing up to 15 times the proportion of ω-3 fatty acids found in the present North American diet (Simopoulos, 1991, 1999), making many argue that our current diet is relatively deficient in ω-3 and that this may contribute to a number of brain-related disorders (Young & Conquer, 2005). Since mammals cannot directly synthesise DHA, it must be obtained preformed from the diet or from other dietary ω-3 fatty acids that are inefficiently converted to DHA (1–6%) through a series of enzymatic steps, setting the stage for inadequate brain supply of DHA just as local turnover increases and conversion decreases with aging (Bourre, 2004; Young & Conquer, 2005).

Docosahexaenoic acid is highly enriched in the brain, where it is synthesized from precursors in astrocytes and then transported and concentrated in neurons (Moore, 1993; Moore *et al.*, 1991). The structural predominance of DHA in the brain is linked to its functional importance since changes in availability and content influence neural membrane-bound enzyme and ion channel activities, membrane fluidity, LTP, and neurotransmitter release (Horrocks & Farooqui, 2004; Young & Conquer, 2005). While there is considerable evidence indicating a

developmental role for ω-3 fats, dietary deficiency, or reduction, even in old and adult animals impairs learning and readily depletes neuronal membrane content (Barcelo-Coblijn *et al.*, 2003; Catalan *et al.*, 2002). Furthermore, dietary supplementation with DHA readily improves membrane content and neurotransmitter receptors that were adversely affected by dietary depletion (Bourre, 2004; Dyall *et al.*, 2006). In the Tg_{2576} mouse model of AD, reductions in dietary DHA led to decreased brain levels and adversely impacted on Aβ deposition, plaque load, dendritic spine formation, synaptic loss, neurotransmitter receptors, and protein oxidation (Calon *et al.*, 2004, 2005; Lim *et al.*, 2005). In the one study addressing functional outcomes, impaired performance in the Morris Water Maze following DHA depletion was prevented by a DHA replete diet (Calon *et al.*, 2004).

These, and other studies (Akbar *et al.*, 2005), consistently link loss of brain DHA with reduced PI3K/Akt activity resulting in downstream caspase activation and neuronal apoptosis in both wildtype and AD-engineered animals. A link between neuronal survival and DHA is further supported by its ability to promote neurite growth in culture (Calderon & Kim, 2004).

Furthermore, DHA induces anti-apoptotic and neuroprotective, anti-inflammatory gene-expression programs in the brain through conversion to neuroprotectin D1. This less well-known role for DHA was subsequently shown to protect neurons from Aβ-induced neurotoxicity which is highly dependent on promotion of oxidative stress/inflammation (Lukiw *et al.*, 2005; Marcheselli *et al.*, 2003). Dietary ω-3 fatty acid enrichment also attenuates inflammatory responses by shifting production of local inflammatory mediators in the brain such as prostaglandins from pro- to anti-inflammatory forms (Cao *et al.*, 2005), and suppresses adverse age-related changes in cortical interleukin and PI3K activity (Maher *et al.*, 2004).

Taken together, studies indicate that DHA deficiency and IR can work through shared mechanisms to impair neuronal health and survival by interfering with PI3K/Akt signaling and promoting oxidative stress and neuroinflammation. Importantly dietary DHA repletion can improve IRc signaling in insulin-resistant individuals (Taouis *et al.*, 2002), and prevent the development of IR by high-fat feeding in animals (Storlien *et al.*, 1987). These mechanisms work in concert with DHA effects on general membrane function, neurotransmitters and neuronal survival and growth.

Dietary antioxidants of plant origin

Dietary antioxidants scavenge the reactive oxygen species (ROS) responsible for oxidative damage and inflammation. The following section will briefly advance a role for plant-based antioxidants in:

- Improving markers of oxidative stress and inflammation.
- Supporting brain insulin signaling and other cell survival pathways.
- Improving cognitive function in aged and AD-engineered animals.

Epidemiological evidence indicates that serum levels of dietary antioxidants and consumption of food-based antioxidants decreases risk of AD and cognitive decline (Engelhart *et al.*, 2002; Hu *et al.*, 2006; in't Veld *et al.*, 2001; Morris *et al.*, 2002; Stewart *et al.*, 1997; Zandi *et al.*, 2002, 2004). The most abundant dietary antioxidants are a large class of compounds commonly found in plants called polyphenols. Their total dietary intake could be as high as 1 g/day which is substantively higher than that of all other classes of known antioxidants. Although ubiquitous in most plant foods, their main sources are darkly or brightly colored fruits, vegetables and plant-derived beverages such as tea (Scalbert *et al.*, 2005).

Polyphenols not only improve the status of different oxidative stress biomarkers (Williamson & Manach, 2005), but may also directly modulate enzymes involved in signal transduction resulting in modification of redox status of the cell, and activation of survival pathways (Scalbert *et al.*, 2005). For example, green tea polyphenols directly influence many signaling pathways including PI3K/Akt (Mandel *et al.*, 2005; Weinreb *et al.*, 2004) independent

of their antioxidant roles, resulting in reduced Aβ fibril formation, soluble Aβ release, and potent radical-scavenging/anti-inflammatory properties. Similarly, blueberry polyphenols exert high antioxidant capacity, and blueberry-polyphenol enriched rodent diets consistently prevent age-related deficits in learning and memory by decreasing brain ROS levels and altering neuronal signaling (Joseph *et al.*, 2005; Lau *et al.*, 2005).

Greater cognitive benefits associate with consumption of foods with higher antioxidant capacity, such as blueberries, compared with those with lower levels of antioxidants, including spinach and strawberry. Blueberry extract prevented cognitive decline in $Tg_{APP/PS1}$ treated mice and increased ERK and PKC activity – both of which are also regulated by insulin and downstream of PI3K (Joseph *et al.*, 2003). In normal, aged rats blueberry polyphenols increased IGF-1 protein levels which associated with reduced memory errors (Casadesus *et al.*, 2004). Comparable studies in Tg_{2576} mice supplemented with spice-polyphenol curcumin demonstrated potent reductions in Aβ, plaque formation, Aβ fibril formation, oxidative stress, and many pro-inflammatory markers including IL-1β even when administered in aged mice that already possess significant AD pathology (Lim *et al.*, 2001; Yang *et al.*, 2005). Thus, plant-based dietary antioxidants have an important role to play in controlling brain inflammation, influencing beneficial neuronal signaling and behavior, as well as having positive impacts on limiting pathological neurodegeneration. The mechanisms employed by polyphenols, once again, indicate the degree of convergence between diet, inflammation and insulin-related signaling on cognitive function and brain health.

Summary and recommendations related to chronic diet

In summary, chronic diet has important impacts on biologic systems intimately involved in neuronal growth, survival and function which are important to maintaining cognitive function. While a large number of systems, involving IR, inflammatory responses, oxidative stress, and changes to membrane structure and function, are implicated, these systems converge at two critical points: (1) sustainability of insulin and insulin-related cell signaling and (2) limiting inflammation. The dietary components discussed all share the ability to influence these processes, and indeed, can beneficially and adversely influence each other. Thus, common clinical trials which focus on only one nutrient or nutrient class are unlikely to be successful as other adverse consequences of a poor quality diet would minimise effectiveness, arguing for a more global change. That is, a "mixed" approach in dietary interventions allows for protection of these two critical points by simultaneously recruiting multiple systems associated with their protection. Although not well researched, one recent study indicated that a low-fat diet enriched with both DHA and polyphenol extract improved learning in old rats compared with a diet high in saturated fat. Importantly, benefits were only seen in old rats with the combined use of DHA and polyphenols, but not when either component was separately provided (Shirai & Suzuki, 2004).

Human food consumption patterns indicate that diets high in saturated fat usually contain lower amounts of plant matter, and place individuals at increased obesity risk (Davis *et al.*, 2006; Nelson & Tucker, 1996). Since saturated fat and obesity are key promoters of IR and many chronic diseases associated with cognitive dysfunction and AD – including stroke (Honig *et al.*, 2003), diabetes (Arvanitakis *et al.*, 2004; Ott *et al.*, 1999), heart disease (Newman *et al.*, 2005) – these and other studies highlight the importance of maintaining a diet that supports good peripheral health given its close relationship with brain health.

The increased demands imposed by rehabilitation reinforce the importance of making appropriate dietary changes as a prudent and inherently sensible contribution to brain recovery. Based on available evidence, these changes could easily be achieved by consuming an overall healthy diet as defined by many federal guidelines including Canada's Food Guide (Health Canada, 2005), that includes one

serving of fresh, fatty fish per week (salmon, mackerel, tuna), 5–10 servings of darkly or brightly colored fruits and vegetables per day – or as many servings as possible – and limits intake of saturated fat as much as possible (fatty meats and processed foods). For a diet likely to minimize IR that also meets the goals of including fish and plant matter, guidelines of the American Diabetes Association (American Diabetes Association, 2006) should be considered.

Although diet is an important aspect of lifestyle, adequate physical activity is another factor known to be greatly beneficial for cognitive function and supporting neuronal health, and the reader is referred to Chapter 24 by Kramer, Erickson and McAuley in this volume for a good review. Importantly, mechanisms implicated with physical activity, including improved brain oxygen delivery and expression of neurotrophins, including BDNF (Cotman & Berchtold, 2002; McAuley *et al.*, 2004; Vaynman & Gómez-Pinilla, 2005), could function synergistically with diet to support processes essential to the formation of new neural networks, and augment cognitive approaches currently used in rehabilitation.

Role of acute diet

While chronic diet modulates major processes involved in neuronal signaling and synaptic plasticity, thereby setting the tone, or local environment, in which physiologic processes associated with cognitive rehabilitation occur, recently consumed food or meals provide brain with substrates, including glucose, needed to support immediate biochemical pathways involved in neuronal communication. A large body of literature exists demonstrating the benefits of food and/or glucose ingestion, on cognitive performance; unfortunately, the application of this information to rehabilitation programs has not been tested.

In this section, we will make the arguments that:

- The fed/fasted state of an individual is an important contributor to cognitive function – particularly tasks involving the hippocampus.
- Cognitive benefits of food ingestion may result from overlapping influences on blood glucose, insulin, gut hormones and sensory afferents.
- Unlike healthy people, cognitive function in individuals with T2DM is negatively affected by foods that rapidly raise blood glucose, possibly due to greater post-ingestive oxidative stress.
- Ensuring that an individual is in the fed state may be a way to boost performance during rehabilitation sessions, potentially contributing to longer-term outcome.

Many original studies investigating the role of food ingestion on cognition lay in the evaluation of school breakfast programs, where school performance was the most common outcome measure. While these studies generally reported benefits associated with the breakfast programs, results were confounded by the fact that concurrent improvements in other parameters, including school attendance, made it difficult to attribute the benefits to the nutrition intervention alone (Pollitt & Mathews, 1998). Numerous, subsequent studies using placebo-controlled cross-over designs have shown benefits on various measures of cognitive performance following ingestion of a single meal or nutrient across a much broader age-span (Kanarek, 1997). These benefits are likely attributed to both eating per se and the provision of energy, or calories, as well as attributes of individual nutrients, notably glucose.

Importantly, an individual's underlying health status, particularly the presence of T2DM, is an important predictor of the response to ingestion of glucose or carbohydrate-rich foods (Greenwood *et al.*, 2003; Papanikoloau *et al.*, 2006), with a focus on high-quality, low glycemic index carbohydrate foods being particularly important for those with T2DM. The fact that most studies were conducted in the early morning and compared a fasting versus fed (nutrient intervention) condition, attests to the importance of breakfast consumption (Greenwood *et al.*, 2003; Kanarek, 1997). However, at least one study found greater glucose-induced enhancement in cognitive performance among older adults who were tested in the afternoon compared with the

Table 16.3. Evidence associated with memory-enhancing benefits of glucose ingestion.

Intake of moderate (50–75 g), but not high, levels of glucose are associated with improvements in cognitive performance	(Parsons & Gold, 1992)
Subjects with poorer overall levels of cognition, including older adults and those with dementia show greater sensitivity to the benefits of glucose ingestion, compared with age-matched subjects with higher baseline levels of performance	(Craft *et al.*, 1992, 1993, 1994, Hall *et al.*, 1989; Manning *et al.*, 1997; Messier *et al.*, 2003)
Not all cognitive domains are sensitive to glucose administration, with functions associated with the hippocampus and medial temporal lobes, such as delayed verbal memory, showing greater sensitivity	(Manning *et al.*, 1993; Parsons & Gold, 1992)
While both acquisition and retrieval of verbal information are augmented, more robust benefits are attributed to encoding processes	(Manning *et al.*, 1998)
Individuals with poorer overall measures of gluco-regulatory status, including IR, show both lower baseline cognitive performance and greater benefits of glucose ingestion. Thus there is a somewhat paradoxical effect of glucose, such that those with decreased abilities to clear blood glucose after ingestion are the very individuals who benefit most from its ingestion	(Craft *et al.*, 1994; Kaplan *et al.*, 2000; Messier *et al.*, 1999)
The benefits of glucose ingestion are no longer evident, and induce memory deficits, when an individual has transitioned from glucose intolerance or IR to overt T2DM	(Greenwood *et al.*, 2003; Papanikoloau *et al.*, 2006)

morning (Greenwood & Winocur, 2005) – a time of day when older individuals are at a circadian nadir in performance (Hasher *et al.*, 1999).

Specifically, the outcome of many studies administering glucose to humans and rats, reviewed in detail elsewhere (Gold, 2005; Korol & Gold, 1998; Messier, 2004), shows benefits associated with glucose ingestion, particularly in tasks associated with the function of the hippocampus and medial temporal lobes and in those with poor underlying memories (for synopsis of evidence see Table 16.3).

Much work has been conducted to understand glucose's mechanism of action. Research demonstrating transient decreases in rat hippocampal, extraneuronal glucose levels during memory-demanding cognitive tasks and its replenishment with glucose administration (McNay *et al.*, 2000) suggests that under conditions of increased neuronal activity local neuronal glucose supply may become limiting. Since glucose supplies energy and also serves as a substrate for synthesis of neurotransmitters such as acetylcholine, glutamate and GABA (Messier, 2004), local glucose depletion may be detrimental to actively firing neurons. Interestingly, the level of hippocampal glucose depletion and improvement in a memory-demanding task was greater in aged animals relative to young adult rats (McNay & Gold, 2001). Since intra-cerebro-ventricular glucose injection produces comparable cognitive benefits to peripherally administered glucose (Lee *et al.*, 1988), results point to a brain-specific benefit of glucose.

Yet, not all benefits of glucose ingestion can be attributed to a localized brain-specific mechanism. For example, administration of fructose, which does not cross the blood–brain barrier, also enhances memory function (Messier & White, 1987; Rodriguez *et al.*, 1994). This fructose-induced improvement in brain function has been attributed to stimulation of afferent vagal fibres. Similarly, others have suggested that eating, in and of itself, through the release of gut peptides, such as cholecystokinin (CCK), can enhance cognitive function either through vagal receptors or blood–brain barrier uptake (Flood *et al.*, 1987; Morley, 1987).

An important confound in many studies of glucose administration is the inability to distinguish between a potential cognitive-enhancing role of

glucose versus that of insulin since glucose administration stimulates pancreatic insulin secretion such that concomitant increases in blood levels of both are observed. Indeed, others have attributed a glucose effect to be mediated via insulin and not glucose per se. For example, glucose-induced enhancement of delayed verbal memory in older adults with AD could be abolished by the co-administration of somatostatin – a compound which suppresses insulin secretion (Craft *et al.*, 1999).

Thus, while it is clear that glucose consumption, mediated either via glucose or an event occurring in tandem with glucose consumption, may enhance memory function in those with poor memories and poor gluco-regulatory status, the question becomes how to translate this experimental approach to humans who consume food and not glucose. The vast majority of dietary glucose is consumed as high carbohydrate-containing foods. Not surprisingly, when older adults consume carbohydrate foods which are rapidly absorbed such as mashed potatoes, producing a similar blood glucose profile to that observed with glucose ingestion (high glycemic index (GI) foods), the same profile of cognitive benefits to that observed with glucose are apparent (Kaplan *et al.*, 2000). Interestingly, however, the consumption of more complex carbohydrate foods, such as barley, which have a minimal impact on blood glucose levels (low GI foods), also enhance verbal declarative memory to the same extent as glucose and high GI foods (Kaplan *et al.*, 2000). Thus it would appear that raising blood glucose levels into an optimal range for cognitive function (Benton *et al.*, 1996; Manning *et al.*, 1993, Parsons & Gold, 1992) is not needed to observe benefits associated with the ingestion of high carbohydrate foods – indeed, the ingestion of healthier, low GI, foods have the same benefit.

The comparable cognitive-enhancing attributes of lower GI carbohydrate foods are important, since consumption of high GI foods, such as white bread and bagels, can have deleterious cognitive effects in those with T2DM (Greenwood *et al.*, 2003; Papanikoloau *et al.*, 2006). The post-ingestive cognitive deficits, especially delayed verbal recall, observed in the T2DM population is highly associated with food-induced increases in blood glucose levels and can be prevented by switching the carbohydrate food from a high GI to a low GI food such as pasta (Papanikoloau *et al.*, 2006). While the mechanisms surrounding the deleterious effects of high GI foods and extreme elevations in blood glucose levels post consumption in those with T2DM are under investigation, results from one study in which a deficit following ingestion of a meal high in fat and simple carbohydrates was prevented by the co-consumption of the antioxidant vitamins C and E suggest that food-induced oxidative stress may underlie some of the negative effects (Chui & Greenwood, in press).

A weakness of many glucose studies relates to the fact that the control treatment was an artificially sweetened beverage such that the impact of consuming energy in and of itself was not controlled for. Consequently, the specificity of glucose's effect could not be evaluated. When we provided older adults with drinks containing equal energy as protein, fat, or glucose, all three macronutrients led to an initial, robust improvement on delayed paragraph recall; however, only glucose ingestion trended toward a sustained improvement on this task (Kaplan *et al.*, 2001), weakly arguing for glucose specificity on measures of verbal memory. Nevertheless, lack of nutrient specificity was apparent in tests of attention and executive function (e.g., Trails Part B) where improvements were observed with all three macronutrients relative to water and better sustained attention, as measured by the elevator task, was observed in adults with T2DM irrespective of whether or not they experienced a hyperglycemia-associated decrement in verbal memory performance following consumption of carbohydrate foods (Papanikoloau *et al.*, 2006).

Collectively, results suggest that cognitive functions associated with the hippocampus and medial temporal lobes likely show a degree of specificity to glucose ingestion, however, other cognitive functions, especially measures of sustained attention and executive function appear more sensitive to the fed-fasted state of the individual.

Summary and recommendations for acute diet

While chronic diet influences processes involved in the longer-term health of neurons, acute diet, or recently ingested food, provide substrates and biologic signals emanating from vagal afferent innervation, that support neurons in their actively firing state. Numerous studies point to the benefits of food ingestion, making it essential to ensure that individuals are not in the fasted state when commencing a rehabilitation session so as to help maximise their performance during the session. Indeed, if sessions are long, it would be prudent to ensure that snacks are consumed periodically to help sustain neuronal needs. While carbohydrate-rich foods have the benefit of providing both energy and glucose, they should have a low glycemic-index to help offset potential decrements in performance that may be apparent in those with T2DM.

Conclusions

While attention has not previously been paid to the potential benefit of diet in cognitive rehabilitation programs, this chapter draws inferences on its importance. Both chronic diet, through its ability to influence neuronal health and survival, and acute diet, through its ability to support actively firing neurons, require attention. It is essential that individuals avoid diets which promote the development of IR, or if present, take aggressive dietary steps to improve their gluco-regulatory status – otherwise the impact of IR, especially if progressed to T2DM, would be predicted to impair synaptogenesis, neurogenesis and overall neuronal survival, thereby limiting the brain's ability to launch physiologic processes needed for cognitive gain. Equally important is that individuals not participate in rehabilitation sessions in the fasted state as neurons would not be bathed in substrate needed to support neuronal activity. Indeed, if sessions are long, planned snacks should be provided to ensure that the brain is adequately nourished throughout cognitive training.

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