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Modulation of memory by insulin and glucose: neuropsychological observations in Alzheimer's disease

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Abstract

Converging evidence has identified a potential association among Alzheimer's disease, glucose metabolism, insulin activity, and memory. Notably, type 2 diabetes, which is characterized by insulin resistance, may modulate the risk of Alzheimer's disease, and patients with Alzheimer's disease may have a greater risk for glucoregulatory impairments than do healthy older adults. In animal studies, it has been shown that raising blood glucose levels acutely can facilitate memory, in part, by increasing cholinergic activity, which is greatly diminished in patients with Alzheimer's disease. Other studies have confirmed that glucose administration can facilitate memory in healthy humans and in patients with Alzheimer's disease. Interestingly, glucose effects on memory appear to be modulated by insulin sensitivity (efficiency of insulin-mediated glucose disposal). Of course, the acute effects of glucose administration should be distinguished from the effects of chronic hyperglycemia (diabetes), which has been associated with cognitive impairments, at least in older adults. The relationship of insulin and memory has been more difficult to characterize. In animals, systemic insulin administration has been associated with memory deficits, likely due, in part, to hypoglycemia that occurs when exogenous insulin is not supplemented with glucose to maintain euglycemia. In healthy adults and patients with Alzheimer's disease, raising plasma insulin levels while maintaining euglycemia can improve memory; however, raising plasma glucose while suppressing endogenous insulin secretion may not improve memory, suggesting that adequate levels of insulin and glucose are necessary for memory facilitation. Clinical studies have corroborated findings that patients with Alzheimer's disease are more likely than healthy older adults to have reduced insulin sensitivity, and further suggest that apolipoprotein E genotype may modulate the effects of insulin on glucose disposal, memory facilitation, and amyloid precursor protein processing. Collectively, these findings support an association among Alzheimer's disease, impaired glucose metabolism, and reduced insulin sensitivity.

Keywords: Alzheimer's disease; Memory; Glucose; Insulin

1. Introduction

Alzheimer's disease, the most common form of dementia among older adults, typically begins with a subtle decline in memory and progresses to global deterioration in cognitive and adaptive functioning. Several neuropathological features are prominent in Alzheimer's disease and may account for changes in behavior. The most studied features include neurofibrillary tangles, senile plaques, cerebral volume loss, and changes in the cholinergic system; however, impaired glucose metabolism and insulin activity also appear to contribute to cognitive decline in patients with Alzheimer's disease. For example, it has been suggested that inhibition of the neuronal insulin receptor may function as an in vivo model of Alzheimer's disease (Frolich et al., 1999; Hoyer and Lannert, 1999; Hoyer et al., 2000). Consistent with this notion, clinical studies have shown that induced hyperinsulinemia while maintaining euglycemia can facilitate memory for patients with Alzheimer's disease and normal adults (Craft et al., 1996, 1999a, 2003). These findings are particularly interesting in light of growing evidence from cross-sectional studies corroborating a relationship between peripheral insulin abnormalities and Alzheimer's disease (Gasparini et al., 2002).

In this review, we will discuss neuropsychological findings that demonstrate a relationship among memory, glucose metabolism, and insulin activity in Alzheimer's disease and

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normal aging. In particular, we will consider evidence that increasing insulin activity and glucose metabolism can facilitate memory for patients with Alzheimer's disease, as well as for healthy older adults, and we will propose potential mechanisms to explain these observations. To set the stage for this review, we turn first to a discussion of memory and then to a discussion of insulin activity and glucose metabolism.

2. Memory and Alzheimer's disease

Declarative, or explicit, memory refers to the conscious and effortful recollection of information. Intact declarative memory is necessary for adaptive functioning and a sense of personal identity in humans. Without adequate declarative memory, a person would not be able to recall important events and appointments, recognize family members or friends, shop for groceries, or remember to take medications or perform personal hygiene activities. Squire and other investigators have demonstrated an essential role in declarative memory for the medial temporal structures, which include the hippocampal formation and the entorhinal, perirhinal, and parahippocampal cortices (Squire, 1992; Squire and Zola, 1996). The hippocampus and adjacent medial temporal cortex are important for learning and recalling facts (semantic memory), as well as for information related to a specific time or place (episodic memory) (Manns et al., 2003b), and for both recall and recognition (Manns et al., 2003a).

The primary diagnostic sign of Alzheimer's disease is a gradual and progressive loss of declarative memory. Initially, the decline is subtle and may not be easily distinguishable from normal age-related changes; however, sensitive neuropsychological tests can detect changes in declarative memory several years prior to the diagnosis of dementia (Backman et al., 2001). Consistent with declarative memory deficits, hippocampal atrophy is a prominent feature of Alzheimer's disease. Predictably, a decline in delayed recall has been associated with hippocampal atrophy for persons with Alzheimer's disease (Kohler et al., 1998; Petersen et al., 2000). Similarly, functional imaging has consistently shown reduced glucose metabolism in the temporal and parietal regions in patients with early Alzheimer's disease and persons at risk for developing Alzheimer's disease (Small et al., 2000). Recently, it was demonstrated that hippocampal atrophy is associated with reduced glucose metabolism in the hippocampus, superior and middle temporal gyri, and the cingulate gyrus, and with increased glucose metabolism in the frontal lobes (Garrido et al., 2002). However, patterns of regional cerebral glucose metabolism may change with the progression from healthy to mildly impaired to severely impaired (Desgranges et al., 2002). Thus, structural and functional deficits in the medial temporal region may contribute to memory loss related to Alzheimer's disease.

3. Insulin activity and glucose metabolism

3.1. In the periphery

Healthy humans and other animals demonstrate a tightly controlled relationship between insulin and glucose metabolism, resulting in relatively small changes in plasma glucose levels through periods of fasting and carbohydrate ingestion. In contrast, in diabetes mellitus the relationship between insulin activity and glucose metabolism is disrupted. The early stages of type 2 diabetes mellitus, the most common form of diabetes, are characterized by hyperinsulinemia and insulin resistance (reduced insulin efficiency); however, hepatic glucose production remains normal, with fasting euglycemia and postprandial hyperglycemia is mild (Ramlo-Halsted and Edelman, 1999). In the later stages of type 2 diabetes, insulin resistance persists, hepatic glucose production rises, and endogenous insulin production falls, resulting in fasting and postprandial hyperglycemia (Ramlo-Halsted and Edelman, 1999).

Many investigators have reported that cognitive deficits are associated with type 2 diabetes (Gregg et al., 2000; Meneilly et al., 1993; Perlmuter et al., 1984; Ryan and Geckle, 2000). Although other investigators have failed to detect deficits (Austin and Deary, 1999; Lowe et al., 1994; Vanhanen et al., 1999), the weight of evidence suggests that verbal memory declines in type 2 diabetes (Strachan et al., 1997). Notably, older adults with type 2 diabetes consistently show list learning deficits (Ryan and Geckle, 2000) and may perform worse than nondiabetic peers on measures of attention, manual dexterity, reasoning, and psychomotor speed (Gregg et al., 2000; Kalmijn et al., 1995; Meneilly et al., 1993; Reaven et al., 1990). Notably, three studies have found that cognitive impairments were ameliorated when diabetes was treated (Gradman et al., 1993; Meneilly et al., 1993; Naor et al., 1997). Additionally, memory may be adversely affected by poor glucoregulation in the absence of diabetes. At least one large population-based study revealed an association between impaired glucose tolerance and cognition. In the Kuopio, Finland study, investigators reported that older adults (mean age = 72.9 years) with persistent impaired glucose tolerance performed worse than did healthy older adults (mean age = 73.3 years) on the Mini-Mental State Examination and on long-term verbal memory from the Buschke Selective Reminding Test (Vanhanen et al., 1998). In a separate study, 36 healthy young adults (mean age = 21.3) were divided into better regulators and worse regulators on the basis of an oral glucose tolerance test (Messier et al., 1999). Relative to better regulators, worse regulators recalled fewer words on a memory test. Collectively, these studies suggest that impaired glucose metabolism and insulin activity are related to the cognitive changes observed in patients with type 2 diabetes.

These findings are informative in the study of cognitive loss in patients with Alzheimer's disease. Type 2 diabetes increases the risk for vascular dementia and may increase

the risk for Alzheimer's disease (Messier, 2003). In the Honolulu–Asia Aging Study, type 2 diabetes was associated with an increased risk for incident dementia, incident Alzheimer's disease, and incident vascular dementia for a cohort of Japanese–American men who were followed for 3 years; however, diabetes alone did not increase the risk for hippocampal neuritic plaques or neurofibrillary tangles (Peila et al., 2002). In the Rotterdam and the Mayo studies, type 2 diabetes increased the risk for Alzheimer's disease, independent of vascular dementia (Leibson et al., 1997; Ott et al., 1999). Conversely, patients with Alzheimer's disease may have an increased risk for aberrations in peripheral glucose metabolism (Meneilly et al., 1993; Razay and Wilcock, 1994). We have reported that patients with moderate-to-severe Alzheimer's disease had elevated true plasma insulin levels, related to healthy older adults (Craft et al., 1998). Collectively, these findings suggest that Alzheimer's disease may be associated with reduced insulin sensitivity (Messier, 2003).

Interestingly, the relationship of abnormal insulin activity and Alzheimer's disease may be moderated by possession of an apolipoprotein (*APOE*) ε4 allele, a genetic factor that increases the risk for Alzheimer's disease (Corder et al., 1993). In the Kuopio study, hyperinsulinemia increased the risk for Alzheimer's disease in persons without an *APOE* ε4 allele (Kuusisto et al., 1997). We have reported that patients without an *APOE* ε4 allele had significantly lower insulin-mediated glucose disposal rates during a hyperinsulinemic–euglycemic clamp, consistent with decreased insulin sensitivity, than did patients possessing the *APOE* ε4 allele (Craft et al., 1998). In contrast, a separate study found that the co-occurrence of type 2 diabetes and the *APOE* ε4 allele may increase the severity of neuritic plaques, neurofibrillary tangles, and cerebral amyloid angiopathy, at least in Japanese American men (Peila et al., 2002). This discrepancy may reflect ethnic differences in the relationship among Alzheimer's disease, type 2 diabetes, and possession of the *APOE* ε4 allele. Together, these findings support the notions that patients with Alzheimer's disease are more likely than healthy peers to have impaired glucose metabolism and insulin resistance, and that these abnormalities may constitute a novel class of risk factors for Alzheimer's disease.

Impaired β-amyloid processing may explain, in part, *APOE* modulation of the association between type 2 diabetes and Alzheimer's disease. β-Amyloid is the primary constituent of neuritic plaques, a hallmark of Alzheimer's disease pathophysiology. Accruing evidence suggests that insulin may modulate levels of β-amyloid by facilitating intracellular β-amyloid release (Gasparini et al., 2001) and by interfering with β-amyloid degradation via insulin degrading enzyme, which is highly expressed in brain (Authier et al., 1996). Convergent findings from independent investigators suggest that insulin degrading enzyme may play a critical role in β-amyloid clearance in brain (Kurochkin and Goto, 1994; McDermott and Gibson, 1997; Qiu et al., 1998). Recently, we reported that hippocampal levels of insulin degrading enzyme were significantly reduced in patients possessing at least one *APOE* ε4 allele, relative to patients without an *APOE* ε4 allele and healthy controls (Cook et al., 2003). Consequently, we hypothesized Alzheimer's patients without an *APOE* ε4 allele may have normal levels of insulin degrading enzyme and increased levels of insulin due to reduced insulin sensitivity, whereas patients with an *APOE* ε4 allele may have decreased levels of insulin degrading enzyme and normal levels of insulin. Presumably, the combination of reduced insulin degrading enzyme activity due to hyperinsulinemia as well as reduced insulin degrading enzyme expression levels associated with possession of the *APOE* ε4 allele could synergistically enhance the risk for developing Alzheimer's disease.

3.2. In the brain

It is well established that insulin and insulin receptors are abundantly but selectively distributed in the rodent brain (Baskin et al., 1987; Havrankova et al., 1978a,b; Unger et al., 1991). Insulin binding is highest in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum. In light of these distributions, insulin may contribute to selective brain functions such as the control of body weight and reproduction (Bruning et al., 2000; Schulingkamp et al., 2000).

Growing evidence suggests that insulin may influence cerebral glucose metabolism in specific brain regions. The brain, fueled primarily by glucose, accounts for ~25% of total glucose metabolism (Magistretti, 2003). To supply brain needs, plasma glucose is transported across the blood–brain barrier (Banks et al., 1997; Baskin et al., 1987; Baura et al., 1993), where, under basal conditions, it is taken up directly into neurons (Pellerin and Magistretti, 1994). However, during physiological activation, glucose is first transported into astrocytes and transformed by glycolysis into lactate. Then, lactate is released by astrocytes and taken up by neurons, where it serves as an adequate energy substrate (Pellerin and Magistretti, 1994).

Glucose transport is mediated by several transporter isoforms: the glucose transporter (GLUT) 1, localized on blood–brain barrier endothelial cells and cortical membranes; the GLUT3 transporter, localized on neurons; and GLUT4 and GLUTx1 transporters, expressed in intracellular compartments of neurons and translocated to cell membranes in response to insulin (Reagan et al., 2001; Schulingkamp et al., 2000). The distributions of specific glucose transporter isoforms vary significantly in central nervous system. Whereas insulin-insensitive GLUT1 and GLUT3 transporters are widespread, insulin-sensitive GLUT4 transporters are selectively distributed. In rats, GLUT4 transporters are expressed in the cerebellum, sensorimotor cortex, hippocampus, pituitary, and hypothalamus (Apelt et al., 1999; Brant et al., 1993; El Messari et al., 1998). Notably, substantial concurrence has been reported for GLUT4 transporter, insulin-containing neuron, and in-

sulin receptor distributions (Apelt et al., 1999). Likewise, GLUTx1 transporters have been observed in the hippocampus and hypothalamus (Ibberson et al., 2000; Reagan et al., 2001). Therefore, the overlapping distributions of insulin, insulin receptors, and GLUT4 and GLUTx1 transporters are consistent with insulin-stimulated glucose uptake in selective brain regions, such as the hippocampus, a structure that supports memory (Apelt et al., 1999).

In contrast, it is unlikely that insulin directly influences GLUT1 and GLUT3 transporters. Although changes in circulating insulin levels modulated GLUT4 expression in brain (Vannucci et al., 1998), hypoinsulinemia did not influence GLUT1 and GLUT3 expression (Badr et al., 2000). Thus, insulin likely does not exert direct effects on plasma-to-brain glucose transport, mediated by GLUT1 and GLUT3 isoforms; however, insulin may exert indirect effects on GLUT1 and GLUT3 transporters via insulin resistance-induced hyperglycemia. In several studies, hyperglycemia decreased blood-to-brain glucose transport, consistent with a down-regulation of GLUT1 transporters (Cornford et al., 1995; Gjedde and Crone, 1981). Collectively, these findings suggest that generalized insulin effects in the brain may be mediated indirectly, for example, by hyperglycemia, and that selective brain sites may be direct targets for insulin action.

4. Glucose and memory: neuropsychological findings

4.1. Glucose and memory: animal studies

At the outset of this section, the distinction needs to be made between acute fluctuations in glucose levels and chronic glucoregulatory impairments. Acute effects of moderate hyperglycemia and hypoglycemia are generally dose-dependent and transient, whereas the effects of chronic glucoregulatory impairments may be persistent. Furthermore, acute and chronic hyperglycemia can produce the opposite effects on memory. Specifically, acute hyperglycemia can facilitate memory, whereas chronic hyperglycemia associated with type 2 diabetes may impair memory, at least in older adults.

The cognitive effects of acute induced hyperglycemia have been examined in many studies, with the consistent finding that raising plasma or cerebral glucose levels facilitates memory. The glucose and memory literature is reviewed extensively in an article in this issue by Messier; however, we will provide a summary of findings that are germane to Alzheimer's disease.

In rodents, peripheral and intraventricular injections of glucose have been shown to produce beneficial effects in a variety of learning paradigms (Flint and Riccio, 1997; Hughes, 2002, 2003; Lee et al., 1988; Messier, 1997; Winocur and Gagnon, 1998). Notably, glucose administration appears to be most effective when administered prior to or immediately following behavioral training, relative to administration after lengthy post-training delays (Lee et al., 1988; Messier, 1997). These findings suggest that glucose facilitates consolidation rather than retrieval of information. Furthermore, glucose effects on memory appear to be dose-dependent, with an inverted U-shaped function (Kopf and Baratti, 1996; Lee et al., 1988; Ragozzino et al., 1996). Given beneficial effects on memory tasks, it is likely that glucose administration contributes to hippocampal functioning. This notion has been corroborated by in vivo microdialysis studies conducted during performance on memory tasks (McNay et al., 2000, 2001).

4.1.1. Cholinergic effects

It is well known that Alzheimer's disease is associated with cholinergic impairments (Mufson and Kordower, 2001). In particular, basal forebrain cell degeneration and decreased choline acetyltransferase levels are prominent features of this disease. Since the cholinergic basal forebrain projects to the hippocampal formation, cell loss in the basal forebrain has implications for the memory functions subserved by medial temporal structures. Based on loss of cholinergic activity, several acetylcholinesterase inhibitors have been widely used to treat patients with Alzheimer's disease. In light of these cholinergic changes, it is important to note that cholinergic activity appears to be associated with the memory-enhancing effects of glucose.

In rodents, cholinergic blockade can impair central nervous system functions, and glucose administration can reverse deficits induced by cholinergic blockade (Kopf and Baratti, 1996; Okaichi and Okaichi, 2000; Ragozzino et al., 1994; Stone et al., 1995, 1998a,b). Additionally, the strength of glucose effects on memory may be related to an animal's sensitivity to cholinergic agents (Messier, 1998). Furthermore, it has been shown that optimal doses of glucose can modulate acetylcholine release (Ragozzino et al., 1996). Thus, glucose effects on both cholinergic activity and memory appear to be dose-dependent. In contrast, it has been shown that lesions of the cholinergic basal forebrain can produce a transient upregulation of cortical glucose transporters in target regions depleted of acetylcholine, corroborating a functional relationship between the cholinergic basal forebrain system and glucose metabolism (Mehlhorn et al., 1998).

While glucose and acetylcholine appear to have a relatively direct association, their effects on memory may also interact with other neurotransmitter systems, for example the γ-aminobutyric acid (GABA) system. It has been shown that septal infusions of the GABA receptor agonist muscimol can decrease extracellular concentrations of acetylcholine in the rat hippocampus and that increasing hippocampal glucose levels can reverse the muscimol-induced acetylcholine decrements in hippocampal extracellular fluid (Degroot et al., 2003).

4.1.2. Effects of age and gender

Age and gender, which alter the risk for developing Alzheimer's disease, likely modulate the relationship be-

tween glucose and memory (Hughes, 2002, 2003); however, age and gender may not act independently. For example, hippocampal levels of choline acetyltransferase activity may show different rates of age-related change in male and female rats. In one recent study, male and female rats had equivalent choline acetyltransferase activity at 5 months, but at 17 and 25 months, choline acetyltransferase activity was reduced in males relative to females (Frick et al., 2002). Given the prominence of cholinergic deficits in patients with Alzheimer's disease, as well as the close relationship between glucose and cholinergic activity, gender-related differences in choline acetyltransferase activity may have implications for glucose effects on memory.

4.1.3. Glucose and memory: summary of animal findings

The beneficial effects of acute glucose administration have been demonstrated in a variety of animal models of learning and memory. These effects are due, at least in part, to changes in cholinergic activity in the hippocampus, although other neurotransmitter systems may contribute to glucose and cholinergic effects on memory. Since deterioration of the basal forebrain cholinergic cells and concomitant changes in cholinergic activity are prominent in Alzheimer's disease, it may be predicted that glucose administration would facilitate memory for patients with Alzheimer's disease, as well as for healthy humans. In the next section, we will examine the effects of glucose on memory in healthy humans.

4.2. Glucose and memory: healthy human adults

A substantial body of findings demonstrates that glucose modulates memory in healthy humans, as well as in other animals. First, we will discuss the effects of acute hypoglycemia, which has been shown to impair memory at plasma glucose levels below 3.0 mmol/l (Mitrakou et al., 1991), and then, we will discuss the effects of acute hyperglycemia.

4.2.1. Acute hypoglycemia

One technique used to study the effects of hypoglycemia is to infuse insulin at a steady rate and simultaneously to infuse glucose at a variable rate. This procedure, the hyperinsulinemic clamp, gives investigators control over the plasma glucose level of subjects. Using this procedure, it has been demonstrated that inducing hyperinsulinemia to approximately 810 pmol/l over a 6-h interval is associated with decreased plasma glucose ($\sim$ 2.4 mmol/l at 6 h) and with increased plasma norepinephrine, epinephrine, growth hormone, and glucagon levels (Mitrakou et al., 1991).

Severe hypoglycemia often will impair higher cortical functioning and may produce disorientation and loss of consciousness. Therefore, it is not surprising that hypoglycemia disrupts a variety of neuropsychological functions, including memory. Mitrakou and colleagues evaluated 10 nonobese, healthy volunteers (mean age = 28 years, mean body mass index = 24 kg/m^2) in a stepped hyperinsulinemic clamp (Mitrakou et al., 1991). Neuropsychological measures included list learning (verbal memory), trail making parts A and B (simple and complex visual attention), simple and choice reaction time, verbal fluency for words beginning with a specified letter, the Stroop test (simple attention and complex frontal inhibition), digit cancellation (controlled visual attention), and forward and reverse digit span (simple auditory attention and auditory working memory). Mean composite scores on the cognitive battery were unchanged at plasma glucose levels of 4.3 and 3.7 mmol/l, relative to baseline plasma glucose; however, composite scores tended to be lower at 3.0 mmol/l and were significantly impaired at 2.3 mmol/l. In addition to verbal memory decrements, specific impairments were seen on verbal fluency, complex attention, simple and choice reaction time, and auditory working memory; however, simple visual attention and simple auditory attention were not impaired.

Other investigators have reported that immediate and delayed visual and verbal memory and working memory are vulnerable to the effects of induced hypoglycemia (Sommerfield et al., 2003), although some studies have failed to detect effects on some verbal memory measures (Fanelli et al., 1998; Widom and Simonson, 1990). Cognitive impairments due to hypoglycemia have been demonstrated in both healthy adults and patients with type 1 (insulin dependent) diabetes mellitus (Widom and Simonson, 1990). Nocturnal episodes of hypoglycemia may pose a special risk for patients with type 1 diabetes, who must take insulin to regulate plasma glucose levels. Patients with nocturnal hypoglycemia were less sensitive to the detrimental effects of induced hypoglycemia on cognitive functioning than were patients with nocturnal euglycemia, suggesting that antecedent nocturnal hypoglycemia may shift symptomatic responses to a lower plasma concentration (Fanelli et al., 1998). Collectively, these findings demonstrate that plasma glucose levels below 3.0 mmol/l may compromise most higher cognitive functions, with the exception of simple attention.

4.2.2. Acute hyperglycemia

This section will provide a brief review of the effects of acute hyperglycemia; see the article by Messier in this issue for a comprehensive review. When glucose levels fall below 3.0 mmol/l, memory and other cognitive functions may be compromised. In contrast, acute hyperglycemia can facilitate non-contextual and contextual verbal memory, visual memory, and other cognitive functions (Allen et al., 1996; Benton and Owens, 1993; Benton et al., 1994; Craft et al., 1992, 1993; Foster et al., 1998; Hall et al., 1989; Manning et al., 1998b; Sunram-Lea et al., 2002). Memory effects are commonly observed with a 25–50 g oral glucose dose (Messier et al., 1998; Parsons and Gold, 1992). As in rodent studies, glucose effects on human memory appear to conform to an inverted U-shaped function. Several additional factors have been identified that may moderate these glucose effects.

4.2.2.1. Glucoregulation, age, sex, and memory. It will be remembered that age and sex modulated glucose effects on memory in rodents. Craft et al. (1994) examined the effects of glucoregulatory response, age, and gender on the ability of glucose to facilitate memory in humans. Twenty-seven young adults (mean age = 20.8 years) and 32 older adults (mean age = 68.5 years) completed cognitive tests after consuming dextrose (50 g) or saccharin on separate days in counterbalanced order. The cognitive battery included measures of verbal memory (story recall, word list recall), visual memory, procedural memory, working memory, verbal fluency, and response inhibition. The investigators used the plasma glucose values during the active metabolic condition to calculate a "recovery index" (final plasma glucose level − baseline plasma glucose level), and then used a median split to divide subjects by age group into subjects with good recovery and subjects with poor recovery. On story recall, older men with good recovery and younger men with poor recovery showed facilitation with glucose administration. In contrast, younger men with good recovery showed deterioration, and older men with poor recovery were not sensitive to glucose ingestion. It is important to note that this recovery index was a relative index within each age group and that older men with good recovery and younger men with poor recovery achieved comparable plasma glucose levels. Therefore, the apparent age effect may also be a surrogate for glucoregulatory efficiency. A likely interpretation of these findings is that the 50-g dose of glucose was maximally effective in facilitating memory for two groups with comparable glucoregulatory efficiency; furthermore, it is possible that the other two groups would have responded differently to a higher or lower glucose dose. Similarly, glucoregulatory status may influence the serial order effect on a story recall task. For example, healthy older adults (> 55 years) were characterized as having good recovery or poor recovery from an oral glucose load (Messier, 1997). Glucose (50 g) improved recall for the initial story items for men with good recovery and decreased recall for those items for men with poor recovery. Furthermore, both studies detected glucose effects on memory for men that were not evident for women.

The relationship of glucoregulatory response and glucose-induced facilitation of memory may be an important factor in examining the effects of glucose on memory in patients with Alzheimer's disease. As we have previously noted, there is increasing evidence supporting an association between Alzheimer's disease and impaired glucose metabolism. Type 2 diabetes may increase the risk for Alzheimer's disease, independent of vascular dementia (Leibson et al., 1997; Ott et al., 1999). Conversely, patients with Alzheimer's disease may have an increased risk for aberrations in peripheral glucose metabolism (Meneilly et al., 1993; Razay and Wilcock, 1994). In light of these findings, patients with Alzheimer's disease may have different dose–response patterns to glucose administration than do healthy older adults, due to reduced glucose sensitivity in patients with Alzheimer's disease.

In summary, an optimal dose of glucose can facilitate memory in healthy humans and other animals. Furthermore, glucoregulatory response, age, and gender may modulate the effects of acute hyperglycemia on memory. In the following section we will review the cognitive effects of glucose administration on adults with Alzheimer's disease.

4.3. Glucose and memory: adults with Alzheimer's disease

Very few studies have examined the effects of acute hyperglycemia in patients with Alzheimer's disease. An early study examined the effects of glucose on cognitive functions for patients with advanced Alzheimer's disease (Manning et al., 1993). In a repeated-measures design, subjects underwent cognitive testing after consuming glucose (75 g) or saccharin. Memory measures included story recall, word list learning, and facial recognition. Glucose significantly improved performance on all memory measures, confirming the hypothesis that acute hyperglycemia can improve memory for patients with Alzheimer's disease.

Craft et al. (1992) examined the effects of glucose and glucoregulatory efficiency on patients with very mild to mild Alzheimer's disease (mean age = 73.5 years) and healthy older adults (mean age = 71.5 years). On separate days in counterbalanced order, subjects consumed glucose (50 g) or saccharin and completed a cognitive battery, which included story recall and verbal paired associates. Relative to controls, patients with Alzheimer's disease demonstrated greater increases in plasma glucose in response to glucose administration, suggestive of less efficient glucoregulation. Patients and healthy adults were then divided into those who demonstrated good and poor recovery from the oral glucose load, determined by plasma glucose concentrations at 75 min following glucose ingestion. Interestingly, glucose facilitated memory in patients with poor recovery and in healthy adults with good recovery. These findings are consistent with the notions that patients with Alzheimer's disease may have a greater risk for impaired glucoregulation, relative to healthy older adults, and that glucoregulatory status may influence the effects of glucose on memory in patients with Alzheimer's disease.

In a longitudinal study, the effects of hyperglycemia on memory and hormones were examined for subjects with very mild or mild Alzheimer's disease and healthy older adults. During the baseline study visits, subjects participated in three counterbalanced glucose conditions on separate days (plasma glucose = fasting levels, 9.7 mmol/l, and 12.5 mmol/l) (Craft et al., 1993). Subjects were tested again after an 18-month interval (follow-up). At baseline, patients with very mild Alzheimer's disease had elevated plasma insulin levels in the fasting and 12.5 mmol/l plasma glucose conditions, relative to other patients and healthy older adults. Interestingly, only the patients with very mild Alz-

heimer's disease showed hyperglycemic memory facilitation on immediate story recall in the 12.5 mmol/l condition. At follow-up, patients who had converted from very mild dementia to mild dementia had the highest insulin responses to both hyperglycemic conditions for both the baseline and the follow-up sessions. At follow-up, patients who had not progressed from the very mild stage of dementia showed hyperglycemic memory facilitation on immediate story recall in the 12.5 mmol/l condition for both the initial and the follow-up sessions. In contrast, patients who had converted from very mild to mild dementia showed less hyperglycemic memory facilitation than did patients who remained at the mild stage, and they no longer showed hyperglycemic memory facilitation on follow-up testing.

Finally, one study investigated the effects of glucose on cognitive functioning for persons with Down's syndrome (mean age = 35 years) (Manning et al., 1998a), a genetic disease that predisposes patients to develop Alzheimer's disease. On separate days, subjects consumed glucose (50 g) or saccharin in counterbalanced order and completed a test battery that included a composite cognitive measure, word list recall, and digit span. Glucose facilitated performance on the word recall and the composite measure, but not on digit span, a test of simple attention. Thus, glucose has been shown to facilitate memory for persons with Down's syndrome, as well as for healthy adults and for patients with Alzheimer's disease.

Collectively, these studies demonstrate that patients with Alzheimer's disease show hyperglycemic memory facilitation; however, it appears that the effects of glucose on memory may be moderated by glucoregulatory efficiency, at least for patients with very mild or mild Alzheimer's disease. Furthermore, there may be an association between the endogenous insulin response to glucose consumption and the memory-enhancing effectiveness of glucose. These findings corroborate the prediction that glucose enhances memory in this population and suggest that dementia status and endogenous glucoregulatory efficiency may moderate glucose effects on memory. These findings also raise the possibility that effective glucose doses may differ for patients with Alzheimer's disease and healthy older adults. These issues will be addressed in the next section.

5. Insulin and memory

5.1. Insulin and memory: animal studies

Animal studies of the effects of insulin administration on memory have produced conflicting results. In general, systemic insulin administration has yielded memory deficits; however, these deficits might have been the result of hypoglycemia due to hyperinsulinemia, given that most investigators did not co-administer glucose to maintain euglycemia. Intraventricular insulin administration has resulted in both memory facilitation and memory impairment. As will be discussed, these conflicting findings may reflect insulin dose–response differences.

5.1.1. Systemic insulin administration

There have been several reports that peripherally administered insulin produced memory impairments in rodents (Clayson, 1971; Kopf and Baratti, 1996; Kopf et al., 1998; Santucci et al., 1990). One study examined the memory effects of insulin and glucose on a step-through inhibitory avoidance task (Kopf and Baratti, 1996). Immediately after training, mice received insulin (48 pmol/kg), glucose (30 mg/kg), or saline and were tested for response latency at 1, 7, and 24 days post-training. At each test interval, glucose increased and insulin decreased step-through latency, consistent with glucose-induced facilitation and insulin-induced impairment of memory. Notably, the investigators reported that the insulin dose was nonconvulsive but did not report plasma glucose levels following insulin administration. Thus, is it difficult to discriminate between the effects of hyperinsulinemia and hypoglycemia on memory.

A subsequent study examined the effects of insulin on open-field exploratory behavior (Kopf and Baratti, 1999). Mice were allowed to explore a chamber for 10 min and then injected with saline or one of three insulin doses (48, 120, 480 pmol/kg). When mice were tested 24 h later, the middle dose (120 pmol/kg) increased test session exploratory behavior, indicative of impaired retention, whereas the lower and higher doses did not elicit significant changes in exploratory behavior. Then, the study was replicated with mice receiving saline or insulin (120 pmol/kg) injected immediately or 3 h after training; immediate but not delayed insulin administration increased test session exploratory behavior, indicative of impaired retention. These results suggest that the effects of insulin, like the effects of glucose, were dose-dependent and occurred during consolidation rather than retrieval of information.

Furthermore, cholinergic changes appear to contribute to the effects of peripheral insulin administration on memory. In a step-through avoidance task study, insulin-induced memory impairments were reversed by the presynaptic muscarinic receptor antagonist 11-((2-((diethylamino)methyl)-1-piperidinyl)acetyl)-5,11-dihydro-6*H*-pyrido(2,3-*b*)(1,4)benzodiazepine-6-one (AF-DX116) (Kopf et al., 1998). Since a presynaptic receptor antagonist should increase acetylcholine release, it is likely that AF-DX116 reversed insulin effects by increasing cholinergic activity. In contrast, simultaneous administration of insulin (48 pmol/kg) and the muscarinic receptor antagonist atropine (0.5 mg/kg) impaired retention after a 24-h delay on an open-field exploratory task, although these doses did not impair retention for either drug alone (Kopf and Baratti, 1999). Finally, on a radial-arm maze test, scopolamine (2 mg/kg) increased memory errors, relative to vehicle, and these errors were reversed by simultaneous administration of scopolamine and insulin (2.4 pmol/kg) or scopolamine and glucose (100 mg/kg) at doses that did not produce

singular effects for insulin or glucose alone (Blanchard and Duncan, 1997). We note that a low dose of insulin attenuated the amnestic effects of cholinergic blockade in this last study, whereas higher insulin doses facilitated the amnestic effects of cholinergic blockade in other studies. It is possible that the lower insulin dose did not induce hypoglycemia and that higher doses did induce hypoglycemia; therefore, the discrepancy potentially reflects differences in plasma glucose concentration. Together, these findings corroborate a role for insulin in the modulation of cholinergic influences on memory.

Caution should be used in interpreting the results of these studies as direct insulin effects, since peripheral insulin administration produces rapid changes in both insulin and glucose levels. Notably, acute hyperglycemia can facilitate cholinergic activity and memory, whereas hypoglycemia due to hyperinsulinemia can impair memory. This observation suggests that hypoglycemia may contribute to reduced memory associated with insulin administration. The finding that glucose (10–1000 mg/kg) administration attenuated the detrimental effects of insulin (48 pmol/kg) on the step-through avoidance task (Kopf and Baratti, 1995) shows that hyperinsulinemic effects on memory can be reversed by raising plasma glucose levels and supports the notion that hypoglycemia induced by hyperinsulinemia contributed to amnestic effects in these studies.

5.1.2. Intracerebroventricular insulin administration

Intracerebroventricular administration of insulin has been shown to raise brain insulin levels without inducing changes in blood insulin or glucose levels (Bernstein et al., 1986). Two groups have studied the effects of intracerebroventricular insulin administration on memory in rodents, with conflicting results. In one study, Long–Evans rats received a chronic third ventricular canula and were trained on a step-through passive avoidance procedure (Park et al., 2000). Animals were removed from the test apparatus and received an intracerebroventricular injection of active insulin (24 pmol), heat-deactivated insulin, or saline. Retention of learning was tested after a 24-h delay. At training, response latencies did not vary for animals in each of the three drug conditions; however, after the 24-h delay, rats that received active insulin showed significantly longer response latencies, relative to rats treated with saline or deactivated insulin. In contrast, response latencies for rats treated with heat-deactivated insulin were not significantly different from control rats. These findings suggest that centrally acting insulin facilitated memory on this passive avoidance task. Furthermore, this study dissociated insulin effects from the effects of hyperglycemia, since blood glucose levels presumably were not altered. The timing of the insulin administration further suggests that memory facilitation occurred as the result of improved consolidation of information.

In a separate study, Long–Evans rats received a chronic lateral ventricular canula and were trained on a step-through passive avoidance procedure (Schwarzberg et al., 1989). Insulin (10 pmol) or saline was administered through the canula 23 h after training, and response latency was tested twice, 24 and 48 h post training. Relative to saline, insulin decreased response latencies at both 24- and 48-h delays. In contrast to the previous study, insulin appeared to produce memory deficits, again presumably without altering plasma glucose levels.

Taken together, these studies demonstrate that intracerebroventricular administration of insulin contributes to memory. Furthermore, the conflicting results may help dissociate the effects of insulin on discrete processes that influence an animal's ability to remember task demands. In one study, memory improved when insulin was administered immediately after training, suggesting that insulin may exert beneficial effects on consolidation of new information. In contrast, when insulin was administered 23 h after training, memory declined. Given the long delay between training and insulin administration, it is improbable that insulin impaired memory due to reduced consolidation of information. Furthermore, insulin dose differences in these two studies may have contributed to the discrepant effects on passive avoidance latency. For example, it has been reported that insulin can dose-dependently inhibit firing hippocampal pyramidal neurons (Palovcik et al., 1984).

5.2. Insulin and memory: human studies

In animal studies, post-training systemic administration of insulin without maintaining euglycemia dose-dependently impaired memory. While it is tempting to interpret these effects as the direct result of insulin action, it seems equally likely that insulin-induced hypoglycemia contributed to memory loss. This interpretation is consistent with the cognitive effects of stepped hypoglycemia observed in healthy adults. Notably, intracerebroventricular post-training insulin injections were associated with facilitation of memory, suggesting that insulin likely contributes to normal memory functions in animals. In this section, we will discuss insulin effects on healthy humans and patients with Alzheimer's disease. These studies used the hyperinsulinemic–euglycemic clamp to avoid the adverse memory effects of hypoglycemia.

5.2.1. Insulin-mediated memory facilitation

Craft et al. (1996) compared the cognitive effects of induced hyperglycemia and induced hyperinsulinemia for 22 patients with Alzheimer's disease (mean age = 71.0 years) and 13 healthy older adults (mean age = 71.8 years). Subjects completed cognitive testing during three counterbalanced metabolic conditions: hyperglycemia (plasma glucose = ~ 12.5 mmol/l), hyperinsulinemia with euglycemia (plasma insulin = ~ 360 pmol/l), and fasting insulin and glucose levels. Cognitive testing consisted of one measure of declarative memory, story recall, and three nonmemory measures, verbal fluency, response inhibition (Stroop Col-

or–Word Interference task), and visuoperceptive judgment. Hyperglycemia and hyperinsulinemia facilitated story recall for patients with Alzheimer's disease but not for healthy adults. Neither metabolic condition altered performance on measures sensitive to frontal lobe function or visuoperception. These findings are consistent with the notion that both hyperinsulinemia and hyperglycemia can selectively facilitate memory for patients with Alzheimer's disease; however, several other issues were raised, notably, whether the discrepant results for patients and healthy other adults reflected a dose–response differences related to disease status. Furthermore, the hyperglycemic condition was also associated with an increase in endogenous insulin secretion, suggesting the possibility that increased plasma insulin may have contributed to the memory-enhancing effects of glucose.

Further evidence of insulin effects on cognition comes from a study that examined the effects of hyperinsulinemia in healthy volunteers (Kern et al., 2001). These young adults (age range 22–32 years) received one of two metabolic conditions, serum insulin raised to either 543 or 24,049 pmol/l during a 6-h infusion protocol. There was no saline control. At baseline and every 90 min thereafter, subjects completed three cognitive measures: a vigilance task (oddball paradigm) as part of auditory evoked potential recording; memory recall for neutral, food-related, and emotional words; and response inhibition (Stroop Color–Word Interference task). On the auditory evoked potential task, the higher insulin dose evoked longer P3 latencies over the frontal and parietal recording sites at 90 and 180 min, relative to the lower insulin dose; latencies were equivalent at 270 and 360 min for both sites. Investigators suggested that these differences in P3 latencies might reflect the action of receptor-mediated insulin transport across the blood–brain barrier; in brief, the lower dose initially produced less dramatic P3 effects but compensated over time, relative to the higher dose. On the memory task, the higher insulin dose facilitated word recall for emotional and food words at 360 min, relative to the lower insulin dose; however, the neutral recall words were not sensitive to insulin dose. This finding is consistent with the notion that this higher insulin dose facilitated recall only for words with increased salience, which may imply that the higher dose acted on brain structures supporting emotionally tagged memory. On the response inhibition task, the higher insulin dose facilitated performance at 360 min, relative to the lower insulin dose. Thus, findings are consistent with insulin dose effects on repeated cognitive testing for a high dose of insulin infused over a sustained period; however, the lack of an inactive control group limits conclusions that can be drawn about the effects of hyperinsulinemia relative to normal blood insulin levels.

Collectively, these studies (Craft et al., 1996; Kern et al., 2001) demonstrate that simultaneous administration of insulin and glucose can facilitate memory; however, they do not answer the question of insulin effects over and above the singular effects of glucose. The observation that glucose administration invokes endogenous insulin secretion further complicates the picture, raising the possibility that elevated insulin levels may contribute to the cognitive effects of glucose administration. To dissociate the effects of insulin and glucose, 23 patients with Alzheimer's disease (mean age = 70.5 years) and 14 healthy older adults (mean age = 69.2 years) completed cognitive testing in each of four counterbalanced metabolic conditions: (1) hyperinsulinemia with euglycemia (plasma insulin = ~ 538 pmol/l, plasma glucose = ~ 5.6 mmol/l), (2) hyperglycemia with endogenous insulin suppressed with octreotide (plasma insulin = ~ 57 pmol/l, plasma glucose = ~ 12.5 mmol/l), (3) suppressed endogenous insulin and fasting glucose levels, and (4) fasting insulin and glucose levels (Craft et al., 1999a). Cognitive measures included story recall and response inhibition (Stroop Color–Word Interference task). For patients with Alzheimer's disease, memory was enhanced during hyperinsulinemia but not by hyperglycemia, demonstrating that suppression of the glucose-stimulated secretion of endogenous insulin can abolish the memory enhancing effects of glucose. Notably, memory was also enhanced when endogenous insulin was suppressed and plasma glucose was maintained at fasting levels. Thus, the singular effects of octreotide did not account for the absence of a memory effect during hyperglycemia. Furthermore, glucose supplementation was not essential to octreotide-induced memory facilitation. Collectively, these findings provide evidence that moderately elevated insulin, in the presence of normal plasma glucose, can facilitate memory in patients with Alzheimer's disease, and further suggest that endogenous insulin secretion during hyperglycemia may contribute to the memory enhancing effects of glucose. Results of this study again demonstrated a discrepancy between patients with Alzheimer's disease, who showed insulin-mediated memory facilitation, and healthy older adults, who did not show this effect at physiological insulin doses.

5.2.2. Alzheimer's disease, insulin levels, and glucose disposal

A previous study examined the effects of glucose administration and glucoregulatory efficiency on patients with very mild to mild Alzheimer's disease and healthy older adults (Craft et al., 1992). Results of this study suggested that patients with Alzheimer's disease had less efficient glucoregulation than did healthy older adults and that glucoregulatory efficiency influenced the effects of glucose on memory in patients with Alzheimer's disease. The following studies corroborate these previous findings by demonstrating insulin abnormalities in patients with Alzheimer's disease.

One study examined neuroendocrine responses to hyperglycemia and hyperinsulinemia in patients with mild and mild-to-moderate Alzheimer's disease and healthy older adults (Craft et al., 1996). As predicted, all subjects showed

increased plasma insulin in response to hyperglycemia; however, the insulin response was exaggerated in patients with mild Alzheimer's disease, who also tended to have elevated plasma norepinephrine levels in response to hyperinsulinemia, relative to healthy controls. Collectively, these findings suggest that patients with mild Alzheimer's have less efficient glucoregulation than healthy peers. A second study also examined the neuroendocrine responses to hyperglycemia and hyperinsulinemia in patients with Alzheimer's disease and healthy older adults (Craft et al., 1999a). Subjects with Alzheimer's disease had elevated plasma cortisol in all conditions, relative to healthy older adults, and insulin administration increased cortisol in patients with Alzheimer's disease but not the healthy older adults. Evidence from a third study further suggests that patients with Alzheimer's disease may have abnormal insulin activity in the central nervous system as well as the periphery (Craft et al., 1998). Cerebrospinal fluid and blood samples were collected from 14 patients with mild Alzheimer's disease, 11 patients with moderate or severe Alzheimer's disease, and 14 healthy older adults. Relative to healthy older adults and patients with mild dementia, patients with moderate or severe Alzheimer's disease had decreased cerebrospinal fluid insulin levels, increased true plasma insulin levels (true plasma insulin = plasma insulin − plasma proinsulin), and decreased cerebrospinal fluid to true plasma insulin ratios. For patients with mild Alzheimer's disease, true plasma insulin levels and cerebrospinal fluid to true plasma insulin ratios were intermediate between healthy older adults and patients with moderate-to-severe dementia, but not significantly different from either group. Taken together, these studies corroborate previous findings demonstrating that Alzheimer's disease may be associated with impaired insulin activity.

Recent evidence points to an association among *APOE* genotype, Alzheimer's disease, and impaired glucoregulation (Craft et al., 1999b; Kuusisto et al., 1997; Peila et al., 2002). Therefore, a natural extension of the work on Alzheimer's disease and glucoregulation was to examine the relationship of insulin activity, glucose metabolism, and Alzheimer's disease in the light of *APOE* genotype.

5.2.3. APOE genotype, insulin activity, and memory

In the cerebrospinal fluid study, patients with Alzheimer's disease were also separated into two groups by *APOE* genotype, *APOE* ε4 homozygotes (subjects possessing two copies of the *APOE* ε4 allele) and *APOE* ε4 non-homozygotes (subjects possessing fewer than two copies of the *APOE* ε4 allele) (Craft et al., 1998). Mini-Mental State Examination scores were equivalent for *APOE* ε4 homozygotes (mean = 16.6) and for *APOE* ε4 non-homozygotes (mean = 17.4), suggesting that these groups did not differ in the severity of dementia. In comparison with healthy older adults, both *APOE* ε4 groups had reduced cerebrospinal fluid insulin levels, although the effect did not reach significance for either group; however, only the *APOE* ε4 non-homozygotes had increased true plasma insulin levels and decreased cerebrospinal fluid to true plasma insulin ratios. Thus, results of this study support the notion that *APOE* ε4 non-homozygotes have a greater risk for abnormal fasting insulin levels relative to *APOE* ε4 homozygotes, despite equivalent cognitive status. Hyperinsulinemic clamp studies extended these findings to demonstrate that *APOE* genotype influences insulin activity in response to induced hyperinsulinemia.

In one study, 31 patients with Alzheimer's disease and 26 healthy older adults completed cognitive testing during each of two counterbalanced metabolic conditions: (1) hyperinsulinemia with fasting plasma glucose (plasma insulin = ∼ 480 pmol/l, plasma glucose = ∼ 5.6 mmol/l) and (2) fasting plasma insulin and glucose (Craft et al., 2000). Cognitive measures consisted of story recall and response inhibition (Stroop Color–Word Interference task). Subjects were divided by disease status (patient, control) and *APOE* genotype (possessing at least one *APOE* ε4 allele, not possessing an *APOE* ε4 allele). For patients but not for healthy older adults, insulin-mediated glucose disposal rates were significantly reduced in the no *APOE* ε4 allele group, relative to the other *APOE* group. Furthermore, hyperinsulinemia facilitated story recall for patients without an *APOE* ε4 allele but not other patients. Finally, investigators examined the effects of insulin and *APOE* genotype on plasma levels of the amyloid precursor protein. Patients without an *APOE* ε4 allele had reduced plasma amyloid precursor protein in response to insulin infusions, whereas patients with an *APOE* ε4 allele had increased plasma amyloid precursor protein in response to insulin infusions. Collectively, these findings support the notion that *APOE* genotype can modulate both insulin activity and insulin effects on memory in patients with Alzheimer's disease.

To determine whether this discrepancy reflected differing dose–response functions, 17 healthy older adults, 17 patients with two *APOE* ε4 alleles, and 17 patients with fewer than two *APOE* ε4 alleles completed cognitive testing during five counterbalanced hyperinsulinemic conditions: plasma insulin raised to ∼ 60 (baseline), 150, 210, 510, and 810 pmol/l, while maintaining euglycemia (Craft et al., 2003). Notably, story recall improved at the lowest plasma insulin level (∼ 150 pmol/l) for healthy older adults and patients who were *APOE* ε4 homozygotes; in contrast, patients who were not *APOE* ε4 homozygotes showed facilitation on story recall at a higher plasma insulin level (∼ 210 pmol/l). Insulin effects on plasma levels of the amyloid precursor protein were also assessed, and a similar shift in dose response sensitivity was observed. An intermediate plasma insulin level (∼ 210 pmol/l) was associated with reduced plasma amyloid precursor protein levels for healthy older adults and patients who were *APOE* ε4 homozygotes; in contrast, patients without an *APOE* ε4 allele showed this effect at a higher plasma insulin level (∼ 510 pmol/l). Collectively, these findings suggest that

those patients who are most likely to show changes in glucose metabolism may also be the least sensitive to the effects of insulin on memory and peripheral amyloid processing.

5.2.4. Insulin, glucose, and memory: the role of β-amyloid

In several studies, insulin modulated amyloid processing in the periphery. It has recently been demonstrated that insulin can modulate amyloid processing in the central nervous system (Watson et al., 2003). During hyperinsulinemic–euglycemic and baseline metabolic clamps, 16 healthy older adults completed cognitive testing, and then cerebrospinal fluid was acquired from each. For the eight subjects older than 70 years, insulin administration raised levels of β-amyloid 42 in cerebrospinal fluid. This clinical finding supports cellular research suggesting that insulin may influence levels of β-amyloid by modulating β-amyloid release (Gasparini et al., 2001) and clearance (Kurochkin and Goto, 1994; McDermott and Gibson, 1997; Qiu et al., 1998). For this older group, insulin-induced changes in story recall and β-amyloid levels were compared; the greatest increases in β-amyloid were associated with reduced memory performance, suggesting that insulin-induced changes in β-amyloid modulated memory. Several reports have described inhibitory effects for β-amyloid on memory in rodents. For example, raising β-amyloid to levels that do not affect the viability of cortical neurons resulted in suppressed phosphorylation of the cyclic adenosine monophosphate response element binding protein (CREB) and interfered with downstream events such as the activation of brain-derived neurotrophic factor (BDNF) (Tong et al., 2001). It has also been proposed that soluble β-amyloid assemblies disrupt memory acutely, purportedly through effects on long-term potentiation (Wang et al., 2002; Westerman et al., 2002). Taken together, these findings suggest that raising insulin levels in the brain can also raise β-amyloid levels, which, in turn, can modulate memory.

5.3. Mechanisms of insulin-mediated memory effects

We have discussed the possible contributions of cholinergic activity and β-amyloid to the effects of insulin and glucose on memory. Memory may also be influenced by insulin-related molecular changes, such as altered insulin receptor expression, and by neurogenesis in medial temporal brain structures.

5.3.1. Insulin and memory: molecular mechanisms

Learning new information appears to alter insulin receptor expression in the hippocampus. When rats received water maze training, a spatial learning task mediated by the hippocampus, insulin receptor expression was rapidly up-regulated in the dentate gyrus and hippocampal CA1 region, and changes were induced in tyr phosphorylation in both cytosolic and membrane proteins (Zhao et al., 1999). Thus, the act of learning may induce functional changes in the hippocampal insulin receptor, such as increased insulin sensitivity.

Furthermore, insulin may modulate long-term potentiation, a cellular model of learning. Long-term potentiation can be induced by activation of the *N*-methyl-D-aspartate (NMDA) receptor, which, in turn, may increase neuronal Ca^{2+} influx. This cascade presumably activates α-calcium-calmodulin-dependent-kinase II (αCaMKII) and other Ca^{2+}-dependent enzymes and eventuates in stronger synaptic associations between neurons (Byrne, 2003). It has been shown that insulin can promote the cell membrane expression of NMDA receptors (Skeberdis et al., 2001), which may increase the likelihood of long-term potentiation induction. In contrast, streptozotocin-induced diabetes (i.e., hypoinsulinemia) reduced α-CaMKII-dependent activity in NMDA receptors (Di Luca et al., 1999), which may decrease the likelihood of long-term potentiation induction. Therefore, insulin may influence learning and memory via NMDA receptor activity.

5.3.2. Insulin and memory: neurogenesis

Neurogenesis, the proliferation of new cells, has been observed in adult humans and other animals (Eriksson et al., 1998; Gould et al., 1999a,b). Furthermore, hippocampal neurogenesis has been associated with spatial learning in rats (Gould et al., 1999a). Notably, simultaneous hypoinsulinemia and hyperglycemia, induced with streptozotocin, reduced neurogenesis in the rat dentate gyrus (Jackson-Guilford et al., 2000). In contrast, treadmill exercise, which did not affect plasma glucose levels, reversed the adverse effects of simultaneous hypoinsulinemia and hyperglycemia on cell proliferation in the rat dentate gyrus (Kim et al., 2003). These findings suggest that reversing hypoinsulinemia potentially can restore impaired neurogenesis. It would be informative to know whether insulin replacement could also modulate this decline in cell proliferation.

5.4. Intranasal administration of insulin

Typically, rodent and human studies have used systemic insulin administration to examine the effects of insulin on memory. The most obvious confound is that raising blood insulin levels increases the rate of insulin-mediated glucose disposal and may lead to hypoglycemia if additional glucose is not supplied. Indeed, in many animal studies, cognitive effects must be attributed to both rising insulin and falling glucose levels. A second confound is the cascade of neuroendocrine changes that follow systemic administration of glucose or insulin. For example, we have reviewed studies in which changes in blood insulin levels were associated with changes in glucoregulatory hormones such as cortisol and catecholamines. In humans, investigators have used the hyperinsulinemic–euglycemic clamp procedure to control plasma glucose levels during hyperinsulinemia; however, this procedure does not prevent the release of

endogenous glucoregulatory hormones. Consequently, results from this procedure do not reflect the singular action of insulin in the brain.

The alternatives for examining the singular effects of insulin are limited. In non-human animals, it is possible to inject insulin directly into the central nervous system. We have reviewed evidence showing that this procedure can modulate memory without influencing blood levels of insulin or glucose. For obvious reasons, intracerebroventricular insulin administration cannot be used with humans, especially vulnerable humans like patients with Alzheimer's disease. Therefore, it is important to develop alternative methods for central nervous system delivery of insulin for humans.

In rodents, intranasal administration of insulin appears to be effective in delivering insulin to the brain without inducing changes in plasma insulin or glucose levels (Thorne and Frey, 2001). Delivery of neurotrophic factors, such as insulin, from the nasal cavity to the brain is rapid, suggesting that these factors are absorbed across the nasal epithelium to the submucosa and then transported along an extracellular pathway into the brain (Thorne and Frey, 2001). Intranasal delivery has been used effectively to transport filamentous phages and neurotoxins to the hippocampus in rodents (Chen et al., 2002; Frenkel and Solomon, 2002), and it has been shown that intranasal administration of growth factors can induce neurogenesis (Jin et al., 2003). These findings suggest that intranasal administration can be used to deliver insulin to medial temporal structures that support memory.

Intranasal insulin administration also appears to be an effective delivery system in humans. In a double-blind, crossover study, 18 healthy young men (age range = 18–34 years) received intranasal administration of biosynthetic human insulin (120 pmol every 15 min) or vehicle, both containing m-Cresol (Kern et al., 1999). Blood glucose, serum insulin, and plasma catecholamine measures were acquired, and subjects performed a vigilance task (oddball paradigm) as a part of auditory event potential testing. Intranasal insulin administration did not affect blood glucose, serum insulin, or plasma norepinephrine or epinephrine levels. In contrast, intranasal insulin administration increased P3 latency and decreased N1 and N3 amplitudes on auditory event potential testing. Taken together, these findings are consistent with the notion that insulin administered via the nasal cavity was active in the brain without appreciable peripheral activity. In a separate study, 36 healthy young adults (age range 25–41 years) received intranasal administration of human insulin (240 pmol) or vehicle and underwent continuous serial collection of cerebrospinal fluid and blood for 80 min after insulin administration (Born et al., 2002). Intranasal insulin administration did not alter serum insulin levels; however, it raised cerebrospinal fluid insulin concentrations and produced an 80% increase in insulin area under the curve. Taken together, results of these studies demonstrate that insulin administered to the nasal cavity is rapidly transported to the brain, most likely by an extracellular pathway (Thorne and Frey, 2001). Therefore, intranasal administration is a prom-

Table 1
Glucose, insulin, and memory in Alzheimer's disease

Alzheimer's disease	May be associated with impaired glucose regulation[a,b]. Patients with Alzheimer's disease may have • Increased plasma glucose levels in response to glucose administration[c] • Increased plasma insulin levels in response to glucose administration[d] May increase risk for insulin abnormalities. Patients with Alzheimer's disease may have • Increased fasting plasma insulin levels[d,e] • Decreased cerebrospinal fluid insulin levels[e] • Decreased cerebrospinal fluid-to-plasma insulin ratios[e]
Acute glucose administration	Can facilitate memory for patients with Alzheimer's disease and healthy older adults[c,d,f,g]; however, glucose-induced memory facilitation can be • Modulated by an individual's glucoregulatory efficiency[c,h,i] • Abolished by suppressing endogenous insulin secretion[j]
Acute insulin administration	Can facilitate memory for patients with Alzheimer's disease and healthy older adults, when fasting plasma glucose is maintained[j,k,l,m,n]. Insulin-induced memory facilitation • Can occur at lower insulin doses for healthy older adults than for patients with Alzheimer's disease[k] • May be suppressed by insulin-induced elevations in cerebrospinal levels of β-amlyoid[n]
Apolipoprotein E (*APOE*) genotype	Moderates the risk for developing Alzheimer's disease[o] and may moderate insulin activity and effects on memory for patients with Alzheimer's disease[e,k,p]. Patients without an *APOE* ε4 allele may • Have reduced insulin sensitivity[p,q] • Show insulin-induced memory facilitation at higher insulin doses[k,p,q] Patients with at least one *APOE* ε4 allele may • Show insulin-induced memory facilitation at lower insulin doses[j] • Have reduced insulin degrading enzyme levels[r]

[a] Meneilly et al., 1993.
[b] Razay and Wilcock, 1994.
[c] Craft et al., 1992.
[d] Craft et al., 1993.
[e] Craft et al., 1998.
[f] Manning et al., 1998b.
[g] Manning et al., 1993.
[h] Craft et al., 1994.
[i] Messier, 1997.
[j] Craft et al., 1999a.
[k] Craft et al., 2003.
[l] Craft et al., 1996.
[m] Kern et al., 2001.
[n] Watson et al., 2003.
[o] Corder et al., 1993.
[p] Craft et al., 2000.
[q] Craft et al., 1999b.
[r] Cook et al., 2003.

ising tool for the investigation of cognitive effects of insulin.

5.5. Summary of insulin effects on memory

Several conclusions are supported by studies presented in this section. First, it appears that raising peripheral insulin levels can facilitate memory when plasma glucose is maintained at normal levels. Furthermore, the endogenous insulin secretion invoked by hyperglycemia may contribute to glucose-stimulated facilitation of memory. Second, some patients with Alzheimer's disease appear to have a greater risk for abnormal insulin activity and glucoregulation than do other patients. This increased risk may be associated with decreased sensitivity to the memory-enhancing effects of insulin. Third, *APOE* genotype, a prominent genetic factor in Alzheimer's disease, appears to modulate both the risk for abnormal insulin activity and for sensitivity to the memory-enhancing effects of insulin. Fourth, the amyloid precursor protein and β-amyloid may be associated with insulin effects on memory and glucoregulation. Finally, novel routes of insulin administration, such as intranasal delivery, may further elucidate the contributions of insulin to memory. (See Table 1 for a summary of insulin and glucose effects on memory in patients with Alzheimer's disease.).

6. Summary and discussion

In this review, we have examined evidence that glucose and insulin play an important role in memory and that abnormal glucose metabolism and insulin activity may contribute to memory loss in Alzheimer's disease. In general, animal and human studies have demonstrated that transient increases in plasma glucose levels can facilitate memory, in part, by modulating cholinergic activity. The relationship of insulin and memory has been more difficult to characterize, largely because systemic insulin administration induces hypoglycemia and promotes a rapid counterregulatory response to dropping blood glucose levels. In contrast, our work has shown that raising plasma insulin levels while maintaining euglycemia can selectively facilitate memory in patients with Alzheimer's disease and healthy older adults. These studies have also suggested that *APOE* genotype may modulate the risk for reduced insulin sensitivity, as well as the effects of insulin administration on memory and peripheral levels of the amyloid precursor protein, which has been associated with Alzheimer's disease pathophysiology. Thus, a growing body of literature supports an association among hyperinsulinemia, insulin resistance, type 2 diabetes, hypertension, and the cognitive impairments seen in Alzheimer's disease.

On a final note, these findings raise an intriguing therapeutic possibility. Improving insulin activity by increasing central nervous system insulin levels facilitated memory for patients with Alzheimer's disease. Thus, medications that improve insulin sensitivity may be effective in treating memory loss in patients with Alzheimer's disease, especially patients who have reduced glucoregulatory efficiency. Ongoing studies are examining the effect of thiazolidinediones, which improve insulin sensitivity, on cognitive functioning. Results of these studies should help determine the therapeutic potential of these medications for Alzheimer's disease, as well as further elucidate the relationship of insulin and memory.

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