Minireview: Mechanisms by Which the Metabolic Syndrome and Diabetes Impair Memory

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Type 2 diabetes is associated with an increased risk of cognitive dysfunction. These effects seem particularly true for memory functions. This article examines how diabetes and the biological changes that occur with diabetes such as hyperglycemia, changes in insulin concentration, hypertension, and changes in lipid levels might lead to these alterations in cognitive functioning, with an emphasis on the mechanisms leading to changes in memory.

Both type 1 (insulin-dependent diabetes mellitus, or IDDM) and type 2 (non-insulin-dependent diabetes mellitus, or NIDDM) diabetes have detrimental effects on cognitive functioning (measures of verbal and numerical reasoning, attention, concentration, verbal and visual memory, and verbal fluency) and may increase the risk of dementia. In type 1 diabetes, chronic hyperglycemia and the recurrence of hypoglycemia appear to be associated with loss of cognitive ability (1–3). A recent review of cognition in type 2 diabetes concluded that despite the poor design and lack of statistical power in many studies, type 2 diabetes appears to be associated with an increased risk of cognitive dysfunction in a wide array of cognitive tests (4). These findings are borne out in larger epidemiological studies (5,6). In particular, in those studies that examined it, loss of verbal memory was most consistently associated with diabetes. This article examines how diabetes and its risk factors might lead to these changes in cognitive functioning, with a particular focus on memory.

Memory

A number of biological structures are involved in learning and memory; the hippocampus and associated areas are thought to be important in this regard (7), although no single brain structure is “critical” in and of itself (8). Similarly, a number of neurotransmitter systems have been implicated, including gamma-aminobutyric acid ergic systems and the cholinergic system. Particular emphasis has been placed on the loss of cholinergic function associated with memory loss in dementia. How might diabetes and its risk factors modulate brain cholinergic mechanisms (9)?

The prevalence of type 2 diabetes increases with increasing age, which itself may be associated with decreased cognitive functioning and may independently account for some cognitive decline. Memory for remote past events appears to be intact with aging. In contrast, encoding and later retrieval of new information is compromised with increasing age. Thus, the negative effects of aging are reflected in a poorer performance in recall and recognition of lists of words or word pairs, memory for short paragraphs, and other verbal stimuli. Examinations of memory in elderly participants with type 2 diabetes have demonstrated a poorer performance in recent memory but not immediate recall (4). Recently, studies concerning the early stages of the disease and in the relatively young have attempted to distinguish the effects of diabetes on cognitive function from those caused by aging. An impaired performance on a battery of cognitive tests measuring immediate and delayed memory, attention, and verbal fluency was observed in non-diabetics with high 2-hour glucose and insulin following an oral glucose challenge (impaired glucose tolerance), which was similar in magnitude to the decrease seen in subjects with diabetes (10). Individuals younger than 55 years old with type 2 diabetes displayed a poorer performance on memory and attention tests than age- and education-matched controls (11). Thus, cognitive impairment may occur in the early subclinical stages of the progression to diabetes and in the relatively young. It would seem that diabetes and impaired glucose tolerance may lead to a decline in memory independently of aging, or alternatively that diabetes or the progression to diabetes represents a state of accelerated aging.

Diabetes, the Metabolic Syndrome, and its Components

Diabetes is a complex metabolic disorder of heterogeneous aetiology. Type 1 diabetes occurs in the young and is characterized by a diminished secretion of insulin. The disease is thought to be autoimmune in nature. Type 2 diabetes is considerably more common and is characterized by insulin resistance. Age and obesity are major factors that contribute to the development of insulin resistance, and it has been estimated that 35% of the variability in insulin action can be explained by these two factors alone (12). The development of diabetes occurs in a number of overlapping rather arbitrary stages; initially or preceding the onset of overt diabetes, there is a period of insulin resistance that is characterized by a compensatory hyperinsulinemia to maintain normal glucose concentrations and the progression from normal to impaired glucose.

Insulin resistance is associated with a constellation of factors termed the metabolic syndrome (also called syn-
drome X or insulin resistance syndrome), which in addition to hyperglycemia, and hyperinsulinemia is characterized by hypertension, dyslipidemia and increased central adiposity. This period may be followed by a deceleration of the system, with a relative decrease in insulin secretion that leads to the onset of overt diabetes. Symptoms associated with advanced diabetes (e.g., peripheral neuropathy) occur in the final stage. Evidence that the early stages described may be associated with changes in cognitive functioning suggest that the metabolic syndrome and its components (see above) may lead to changes in cognition. Although in vivo it is likely that the mechanisms discussed below act in concert with each other, for ease of discussion, the contributions of metabolic disturbances and hypertension are discussed separately here.

The metabolic disturbances that occur in the metabolic syndrome are (a) hyperglycemia, (b) hyperinsulinemia, and (c) dyslipidemia. Additionally, hypertension is a component of the metabolic syndrome. Each will be discussed in turn.

**Hyperglycemia**

Both increases and decreases in glucose concentrations can potentially alter cognitive function. The detrimental effects of hypoglycemia on cognitive function are well documented. Both acute and chronic hypoglycemia in type 1 diabetes are associated with declines in measures that test intellectual functions and reaction time (1,13,14). In contrast, acute hyperglycemia might be expected to improve memory, as glucose, in addition to its metabolic function, acts as a substrate for acetylcholine and other neurotransmitters involved in memory and other cognitive processes (15,16). However, a number of lines of evidence suggest that chronically raised glucose concentrations lead to decreased cognitive functioning; poor glycemic control is associated with poor learning and memory, and the pharmacological improvement of glycemic control improves cognitive function test performance in older adults, although it is unclear whether this is due to glucose control or to the pharmacological intervention (17). Animal studies suggest mechanisms by which raised glucose might induce these changes. Chronic, but not acute, hyperglycemia induced by streptozotocin leads to a decrease in acetylcholine synthesis and release in the brain of rats (18). Chronic hyperglycemia in rats also produces a significant loss of cortical neurons and, paradoxically, relative neuroglycopenia induced by decreased glucose transfer across the blood–brain barrier. Loss of cortical neurons would result in cognitive impairment, as memory is thought to be “stored” in the cortex (8) and neuroglycopenia would result in decreased glucose availability as a substrate for acetylcholine. As noted previously, decreased cholinergic transmission would result in impaired memory.

**Hyperinsulinemia**

Insulin concentrations rise initially in the natural history of type 2 diabetes to compensate for defective insulin action, whereas in type 1 diabetes insulin secretion is diminished, leading to treatment with exogenous insulin administration. In some cases, insulin is also administered in the later stages of type 2 diabetes. Both animal and human studies provide evidence of a role for insulin in the impairment of a wide range of cognitive functions. High peak insulin response to glucose load has been found to be negatively correlated with learning ability in rats (19). In a study of over 5,500 subjects, direct effects of insulin on cognitive function were proposed. Serum insulin concentrations 2 hours following glucose challenge were associated with a poorer performance on the mini mental state examination (MMSE) (20) in nondiabetic women without dementia independently of cardiovascular risk factors and glucose levels (21). In elderly subjects with persistent impaired glucose tolerance, fasting insulin was associated with a poorer performance on the MMSE and in a test of long-term memory (10). Insulin treatment has also been associated with poorer performances in tests of verbal and visual memory (6). However, these data should be treated with caution, as insulin treatment occurs in severe diabetes that is resistant to other forms of treatment and thus may simply be a proxy for severity of diabetes. The effects of insulin in this regard require further investigation.

A number of mechanisms can be postulated by which insulin might alter cognitive functioning. Serum insulin concentration is significantly associated with cerebrospinal fluid insulin, as insulin is transported across the blood–brain barrier (22). Insulin receptors are present in the hypothalamus and hippocampus and mediate a decrease in cholinergic transmission (23,24). Hyperinsulinemia is also a risk factor for atherosclerosis, which is associated with cerebrovascular disease. However, although a direct effect of insulin on cognitive function is plausible, the role of a chronically increased insulin secretion in the context of diabetes is unclear, because hyperinsulinemia is not always apparent in type 2 diabetes. This is especially true in the later stages of the disease, when glucose toxicity may actually mediate diminished insulin secretion. The possible role of insulin in cognitive decline associated with diabetes therefore remains unclear and requires further investigation.

**Dyslipidemia**

Dyslipidemia is associated with the insulin resistance syndrome. A limited number of studies have suggested a role for raised triglyceride levels in cognitive impairment. Triglycerides are inversely associated with verbal fluency both cross-sectionally and prospectively (25) in diabetic patients. Hypertriglyceridemia in elderly patients with type 2 diabetes is associated with a decline in reaction times and backward digit span independently of any changes in glucose concentrations (25). High serum triglyceride levels are also associated with slower reaction times in a series of tests and with decreased verbal fluency in a small group of elderly subjects with normal glucose tolerance (26). Cognitive performance is also improved in patients treated with a triglyceride-lowering compound, gemfibrozil. Raised triglyceride concentrations are associated with atherosclerosis, and so the mechanism to alter cognition may be similar to that discussed for hypertension. Elevated triglyceride levels may also affect cognitive performance by increasing blood viscosity and impairing its rheological properties (27), which in turn might alter cerebral perfusion and accelerate atherosclerosis. In support of this hypothesis, a recent report has de-
scribed a small negative association between delayed word recall and plasma fibrinogen in a cohort of 14,000 middle-aged adults (28). Furthermore, there is tentative evidence from the findings that antithrombotic treatment (with aspirin or warfarin) is associated with better verbal fluency and mental flexibility (29).

Hypertension and Cognitive Function
Raised blood pressure is a risk factor commonly associated with insulin resistance syndrome and type 2 diabetes and has been the focus of much research on changes in cognitive function. There is a reduction in learning in spontaneously hypertensive rats, the most widely used animal model of essential hypertension, which is additive with that seen with age (30). This suggests that hypertension alters aspects of cognition. However, until recently the role of hypertension in cognitive impairment was equivocal in humans; as some studies found an association (31) whereas others did not (32). More recent studies examining the effects of raised blood pressure on changes in cognition over time have shown that hypertension does indeed lead to cognitive impairment. A recent report has demonstrated that type 2 diabetes and high blood pressure are independently associated with poorer performances on tests measuring immediate and delayed memory for prose and that higher diastolic blood pressure is associated with poorer performances on a measure of verbal fluency (6). In another study of nondiabetics, hyperinsulinemia in hypertension was associated with poor performances in cognitive tests reflecting calculation and verbal fluency (33). High diastolic blood pressure in men aged 50 years was also found to be associated with poorer performances on the MMSE 20 years later (34). How might hypertension cause changes in cognitive function? Again the cholinergic system can be implicated as, in the spontaneously hypertensive rat, decreased nicotinic receptor sensitivity to acetylcholine has been observed (35,36). A further mechanism that can be postulated is that hypertension is known to be associated with cerebrovascular disease, lacunar brain infarct, and brain white matter lesions. These alterations can be incurred directly or indirectly, for example, through accelerated atherosclerosis (37). Impaired cognitive performance in hypertension is associated with white matter lesions when an assessment is made by magnetic resonance imaging (38).

Dementia and Insulin Resistance and Diabetes
Most cognitive declines with advancing age, though the progression of mild cognitive impairment to dementia is not the most common evolution. The evidence is inconclusive as to whether cognitive impairment and dementia exist on a continuum or represent distinct processes (39). It is unclear whether the factors or processes that affect cognitive decline are the same as those that predict dementia. Dementia can be broadly split into two types; Alzheimer’s type and vascular dementia. Alzheimer’s disease (AD) is a degenerative brain disorder characterized by neuronal and synaptic degeneration and an increased number of senile plaques and neurofibrillary tangles compared with nondemented individuals of the same age. AD involves substantial loss of elements of a number of transmitter systems, the best described of which is the cholinergic system (40). AD is characterized by decreased brain glucose turnover, which results in decreased cholinergic transmission and memory impairment. The causes and pathogenesis of its most common form are multifactorial and are largely unknown. Vascular dementia is less common and is caused by cerebrovascular and ischemic brain damage, that is, a combination of multiple cerebral infarcts, lacunas, and ischemic white matter lesions, a demyelination of the periventricular white matter.

One of the best known risk factors for developing Alzheimer’s disease is carrying the ε4 allele of the apolipoprotein E (Apo ε4) gene, but it is not necessary to carry the Apo ε4 allele to develop Alzheimer’s disease (41). Recent studies have reported an association between features of the insulin resistance syndrome (hyperglycemia and hyperinsulinemia) and newly detected Alzheimer’s disease (5,42). Incidence of AD reported in this study was as high in the insulin resistance group as in the carriers of the Apo ε4 allele (42). In addition to the mechanisms by which hyperglycemia might lead to cognitive impairment discussed above, it can be hypothesized that hyperglycemia might mediate accelerated progression of AD by means of advanced glycation end-products (AGEs). These are products of glycation of proteins, and they accumulate in tissues as a function of time and blood glucose concentrations. They are found in amyloid plaques of AD (43) and are thought to accelerate the plaque deposition that occurs in AD. Thus, hyperglycemia and hence an increased production of AGEs may contribute to the formation of amyloid plaques in AD. This hypothesis requires further investigation.

Vascular dementia is caused by cerebrovascular and ischemic brain damage. Several lines of evidence suggest that multiple infarcts and ischemic white matter lesions associated with hypertension are vascular causes of dementia. Performances on the MMSE were worse in a hypertensive group with white matter lesions than in the normotensive group and hypertensive group without such lesions. White matter lesions also occur in Alzheimer’s disease, indicating a role for hypertension in the etiology of both types of dementia. Hypertension and white matter lesions are strongly implicated in the etiology of a particular dementia syndrome, Binswanger’s syndrome (44). A recent longitudinal study reported that raised blood pressure predicted the incidence of both vascular dementia and Alzheimer’s disease after 15 years (45,46), suggesting that hypertension is indeed a risk factor for dementia.

Conclusions
There is now substantial evidence to support the conclusion that type 2 diabetes is associated with memory impairment and dementia. These alterations in cognitive function may represent accelerated aging in diabetes, although evidence in this regard is poor. There is literature suggesting that both the metabolic control and the hypertension that occurs as a consequence of diabetes are involved in the etiology of the cognitive impairment that may occur. The literature on the mechanisms with regard to cognitive impairment is unclear. Evidence suggests a role for glycemic control in both memory decline and dementia. The role of insulin, hypertension,
and dyslipidemia in loss of memory functions is less convincing, although these factors are associated with decline in other functions such as verbal fluency. Their role in dementia is also apparent. It is unclear if these factors are using the same or different mechanisms to cause these changes in cognition. It is possible that different pathways may converge in the case of dementia. The literature describing cholinergic transmission and factors associated with diabetes has been highlighted in this article. A number of transmitter pathways that are associated with memory and cognitive functioning have not been discussed. More research is needed to further characterize these mechanisms. The association between factors associated with diabetes and cognitive function as well as dementia provides the individual with means to control the onset of these consequences of aging and pathology by modification of lifestyle and behavior.

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References


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