Toward a Model of Memory Enhancement in Schizophrenia: Glucose Administration and Hippocampal Function

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Introduction

The reduction of positive symptoms (ie, hallucinations and delusions) has traditionally been the main goal of pharmacological treatments for schizophrenia. Even as first- and second-generation antipsychotic medications allow many patients to approach that goal, however, residual disabilities involving neuropsychological and other clinical problems (eg, negative symptoms) continue to prevent patients from assuming functional, independent lives.1–5 While some antipsychotic medications may improve aspects of cognition (eg, Harvey and Keefe,6 Sharma and Mockler,7 Green and Braff8), the effects are modest3 and leave substantial deficits.2,9,10 These deficits, particularly in verbal declarative memory, sustained attention, and executive dysfunction, predict the disabilities in social problem solving, performance of daily/occupational activities, and acquisition of psychosocial skills that contribute to incomplete recovery in most patients.1–5,8

This problem highlights a growing consensus about the need for novel treatment approaches to target cognitive deficits independent of clinical symptoms,3,11–13 and raises the question of how to proceed. Thus far, the search for antipsychotic medications that also improve cognition continues to dominate the field, with the modest outcomes noted above. Another approach involves the development of focused treatment strategies that are adjunctive to, but independent of, antipsychotic medications, as is reflected in the National Institute of Mental Health (NIMH)–sponsored Treatment Units for Research on Neurocognition in Schizophrenia initiative. This article emphasizes the adjunctive approach and proposes a systematic exploration of brain mechanisms that might facilitate the development of cognitive enhancers in schizophrenia. Although numerous conceptual criteria might be utilized to guide the search for cognitive enhancers, the current discussion will focus on 4 that are likely to be useful. The first issue is to select one or more cognitive domains that are impaired in schizophrenia. In this discussion, dysfunction in long-term verbal declarative memory will be emphasized. The second issue involves the current status of preclinical and clinical efforts to improve declarative memory using antipsychotic medications, which is the main existing mode of treatment.

Recognition of the need to treat cognitive deficits in schizophrenia is compelling and well established, with empirical findings and conceptual arguments related to cognitive enhancement appearing regularly in the literature. Cognitive enhancement itself, however, remains at an early stage. Biological approaches have centered on the development of antipsychotic medications that also improve cognition, but the results have so far remained modest. As a way to facilitate the development of cognitive enhancers in schizophrenia, this article focuses on adjunctive pharmacological approaches to antipsychotic medications and highlights the need for systematic explorations of relevant brain mechanisms. While numerous conceptual criteria might be employed to guide the search, we will focus on 4 points that are especially likely to be useful and which have not yet been considered together. First, the discussion will focus on deficits in a particular cognitive domain, verbal declarative memory. Second, we will review the current status of preclinical and clinical efforts to improve declarative memory using antipsychotic medications, which is the main, existing mode of treatment. Third, we will examine an example of an adjunctive intervention—glucose administration—that improves memory in animals and humans, modulates function in brain regions related to verbal declarative memory, and is highly amenable to translational research. Finally, a heuristic model will be outlined to explore how the intervention maps on to the underlying neurobiology of schizophrenia. More generally, the discussion underlines the promise of cognitive improvement in schizophrenia and the need to approach the issue in a programmatic manner.

Key words: cognitive enhancement/antipsychotic medication/medial temporal lobe

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Verbal Declarative Memory and Schizophrenia

Overview

Verbal declarative memory is one of the several cognitive domains that have been studied extensively in schizophrenia. Performance in this domain involves the conscious recall and recognition of facts and episodes and also involves memory for relationships between different elements or dimensions of information. Among several brain regions that contribute to verbal declarative memory, the hippocampal region is among the most critical. From a functional perspective, deficits in verbal declarative memory are highly significant and contribute to difficulties in performing activities of daily living in multiple disorders and conditions, including, eg, Alzheimer disease. Deficits in verbal declarative memory in schizophrenia also contribute significantly to the difficulties in independent living and poor clinical outcomes described above, which underscores their importance as potential treatment targets.

Nature and Extent of Deficits

Cognitive problems are central to schizophrenia and affect the course and outcome of the disorder adversely. They often occur well before psychosis, near the first psychotic episode, and after remission from psychotic symptoms. Neuropsychological profiles in patients usually include widespread impairments. Deficits in verbal declarative memory are well established. More than 110 studies reviewed by our research group recently showed they are among the most robustly abnormal deficits in schizophrenia, with effect sizes that often exceed 1.0 SD. The nature of the dysfunction is heterogeneous. Some studies, eg, reported deficits in acquisition/encoding, memory storage (ie, abnormal forgetting), and retrieval, while others reported significantly abnormal rates of forgetting, at least in a portion of the sample. Most subjects with schizophrenia show rates of forgetting that are only subtly impaired relative to control subjects and are more like controls than they are like patients with Alzheimer disease. They do show prominent deficits in retrieval of information using free recall paradigms and/or difficulties encoding new information but better performance on cued or recognition conditions. Although some medications administered to patients with schizophrenia may themselves contribute to performance deficits in tests of verbal memory, the presence of memory deficits before or near the first psychotic episode reflects their intrinsic nature. Nonpsychotic biological relatives of patients with schizophrenia (who are not taking antipsychotic medication) also perform worse on encoding (but not rate of forgetting) than controls on tests of verbal declarative memory (Cirillo and Seidman; Faraone et al; Faraone et al; Faraone et al; Kremen and Hoff; Stone WS, Tsuang MT, Faraone SV et al, unpublished data), which further supports the view that impairments in learning and memory reflect intrinsic features of the disorder rather than epiphenomena related to effects of medication, psychosis, or other cognitive dysfunctions.

Neurobiological Correlates of Deficits in Declarative Learning and Memory: the Hippocampal Region

The hippocampal and parahippocampal areas are particularly important to the instantiation of verbal declarative memory and to related processes such as sensory information processing, context analysis, and sensory gating (eg, Eichenbaum, Freedman et al). Morphometric and neurohistological studies strongly implicate abnormalities in temporal limbic and prefrontal structures in schizophrenia including reduced volume in patients and in nonpsychotic, first-degree relatives of patients. Bilateral abnormalities are most common but are relatively greater on the left side. These findings are consistent with the hypothesized importance of temporal lobe structures in schizophrenia not only in relation to cognitive dysfunction but also to psychosis and other clinical dimensions that characterize the disorder. In contrast, bipolar disorder is not generally associated with reduced hippocampal volumes though with exceptions.

Impaired Hippocampal Recruitment and Function

Impaired hippocampal “recruitment” in schizophrenia during conscious recollection is particularly consistent with reduced hippocampal volume. Seidman et al reported significant and positive correlations between verbal memory performance and hippocampal volume (ie, smaller volumes were associated with poorer memory performance). Unlike most pathological conditions that involve the hippocampus and memory (eg, Alzheimer disease, stress-related conditions), there is less evidence of hippocampal cell loss (with exceptions, such as...
as Benes et al\textsuperscript{64} but more evidence of decreased dendritic arborization, fewer neuronal connections, and less gene expression for molecules likely to be involved in neuronal plasticity (eg, non-N-methyl-D-aspartate glutamate receptors, synaptophysin, SNAP-25, synapsin, complexin I and II, and GAP-43).\textsuperscript{59,60} To an extent, hippocampal abnormalities in schizophrenia are not specific. Although the hippocampus in bipolar disorder is not typically smaller, eg, many similar neurochemical anomalies characterize both conditions.\textsuperscript{75} particularly in regions that are involved in the type of synaptic plasticity that is important for learning and memory (CA 3 and CA 4).\textsuperscript{53} One interpretation of these findings is that smaller hippocampi in schizophrenia reflect fewer synaptic connections and less “pressure” than normal to respond to experience with adaptive synaptic remodeling and other forms of neuronal plasticity.\textsuperscript{56} An implication of this interpretation is that hippocampal function in schizophrenia is thus inefficient. This view is at least consistent with the empirical findings that information is harder to learn and to retrieve, although memory storage itself is not usually the main problem. It is unclear whether genetic and neurophysiological abnormalities alone are sufficient to account for memory impairments in schizophrenia. As will be suggested below, a combination of factors may be necessary to produce observable deficits.

Prefrontal Cortex and Medial Temporal Lobe Connectivity

A detailed discussion of the role of the prefrontal lobes in verbal declarative memory is beyond the scope of the current article. It should be noted, however, that multiple prefrontal brain regions mediate verbal declarative memory in addition to the hippocampal system,\textsuperscript{76–78} and are also involved in working memory. These regions, and possibly the connections between frontal and temporal regions, are often abnormal in schizophrenia\textsuperscript{58,79–83} and are associated with verbal declarative memory.\textsuperscript{84} Moreover, frontal lobe pathology is associated with impaired performance on recall and recognition of episodic information.\textsuperscript{77,85} In this light, one or more underlying prefrontal processes, such as processing speed,\textsuperscript{86} selection of efficient task strategies,\textsuperscript{78} and the representation, maintenance, and updating of context information to control behavior,\textsuperscript{81,87} in concert with other factors such as attention span and motivation, likely contribute to prefrontal dysfunction, which then contributes to deficits in learning, retaining, and retrieving information. Implications of overlapping neurobiological and cognitive substrates for conceptually separate cognitive processes are (1) interventions that modulate function in l cognitive domain (eg, verbal declarative memory) may also modulate function in other domains (eg, working memory) and (2) cognitive function in a particular domain may be manipulated either directly or through manipulation of a related cognitive function.

Enhancement of Verbal Declarative Memory in Schizophrenia

Antipsychotic Medication Effects on Cognition

Until the advent of newer “atypical” antipsychotic medications, few improvements in cognition were associated with pharmacological treatments for schizophrenia,\textsuperscript{88} though this has been debated recently, particularly when appropriately low doses of typical antipsychotic medications were used.\textsuperscript{89} In 1 recent meta-analysis,\textsuperscript{90} 17 of 23 studies demonstrated relatively superior performance of atypical antipsychotics on long-term memory, but the average difference vs typical antipsychotics (measured in SDs) was small (0.17). Nevertheless, at least some improvements in cognitive function are associated with atypical antipsychotic administration (eg, Sharma and Mockler,\textsuperscript{7} Green and Braff,\textsuperscript{9} McGurk,\textsuperscript{9} Stip,\textsuperscript{91} Keefe et al,\textsuperscript{92} Meltzer and McGurk,\textsuperscript{93} Kern et al,\textsuperscript{94} Purdon et al,\textsuperscript{95} Harvey and Keefe,\textsuperscript{96} Harvey et al,\textsuperscript{97} Weickert and Kleinman,\textsuperscript{98} Velligan et al,\textsuperscript{99} Keefe et al\textsuperscript{100}). Although such gains are encouraging, the improvements are modest (with effect sizes usually <0.5) and substantially smaller than the usual deficit of 1.0–1.5.\textsuperscript{9,10,23} Notably, the range of improvement tends to be broad, with facilitation reported often in multiple cognitive domains (eg, Purdon et al,\textsuperscript{95} Harvey et al,\textsuperscript{97} Velligan et al\textsuperscript{99} Keefe et al\textsuperscript{100} Weickert\textsuperscript{101}). Consistent with the pharmacological actions of these medications on multiple neurochemical systems, their actions on multiple aspects of cognition reflects their widespread effects on brain function.\textsuperscript{102}

Similarly, pharmacological treatments administered in addition to antipsychotic medications that show promise to improve memory performance involve multiple neurochemical effects. These include, eg, rivastigmine and donepezil, both of which are cholinesterase inhibitors\textsuperscript{103,104} (but see also [Friedman et al,\textsuperscript{105} Tual et al,\textsuperscript{106} Freudenreich,\textsuperscript{107} Kumari et al\textsuperscript{108} for negative findings with donepezil), L-tryptophan, an amino acid precursor of serotonin,\textsuperscript{109} Ondansetron, a serotoninergic 3 antagonist,\textsuperscript{110} mianserin, a serotoninergic 2A antagonist,\textsuperscript{111} and modafinil, whose actions include histamine release.\textsuperscript{112} Moreover, adjunct pharmacological treatments that may improve other aspects of cognition in schizophrenia, such as attention, appear to do so through diverse neurochemical pathways. These include, eg, guanfacine, an alpha 2 adrenergic agonist,\textsuperscript{113,114} amphetamine, a monaminergic (ie, dopamine, serotonin, and norepinephrine) reuptake inhibitor,\textsuperscript{115–117} modafinil,\textsuperscript{112} and rivastigmine.\textsuperscript{103} Some of the drugs listed here (rivastigmine, modafinil) may influence both memory and attention/working memory (among other functions), consistent with the multiple effects demonstrated by antipsychotic medications on cognition. So far, studies demonstrating positive effects of antipsychotic medications on cognition are largely limited
to studies with humans. Studies with animals (rodents, usually) either do not show facilitation or even show impairment. Studies that do demonstrate facilitation in animals tend to involve attention, rather than memory. Conceptually, it is not necessary for an antipsychotic drug to improve cognition in animals in order to predict cognitive improvement in humans or to modulate biological systems that are related to enhanced cognition in people. Nevertheless, the lack of corresponding effects on tests of memory inhibits the development of useful animal models of pharmacological enhancement and slows down the development of translational research.

Multiple Neural Systems and Cognitive Enhancement

The ability of antipsychotic medications and adjunct treatments to modulate multiple aspects or domains of cognition in schizophrenia is consistent with a broader literature showing the multifactorial nature of cognition itself at both behavioral and neurobiological levels. Three related points are particularly relevant to the present discussion. First, interacting neurochemical substrates underlie the performance of most cognitive tasks (eg, White and McDonald, Poldrack and Packard, Gold, Myhrer). Thus, similar to the effects of antipsychotic and adjunct medications, manipulations of different neurochemical systems often influence performance on the same tasks. These results are consistent with our own previous findings in mice showing that scopolamine (a muscarinic cholinergic antagonist, administered systemically)-induced impairments in memory were reversed not only with cholinergic agonists (physostigmine, oxotremorine) but also with adrenergic agonists (amphetamine, epinephrine) and glucose. Similarly, systemic glucose and physostigmine administration attenuated nonmnemonic behavioral alterations (ie, locomotor hyperactivity) induced by morphine and amphetamine. Second, these neurochemical systems contribute to the formation of neural systems that process and store certain types of information. Although several of these systems are capable of processing information independently of the others, they usually interact. Third, the nature of these interactions between different neural systems varies. Multiple systems of memory, eg, may be cooperative or competitive with each other.

Several hypotheses may be derived from these findings. First, enhancement of a particular cognitive function does not necessarily have a discrete “solution.” Rather, modulation of neural systems that subserve a particular cognitive function may be achieved through modulation of more than 1 neurochemical system. Second, among neural systems that subserve tasks or components of cognitive tasks, the modulation of some of these systems will be more efficient for performing the task than will the modulation of other systems. In a task involving verbal declarative memory, eg, cognitive enhancement might involve the relative activation of neural systems that process that type of information most efficiently (eg, the hippocampal and parahippocampal regions). It will thus be important to select or develop treatments that target particular neurotransmitters represented in selected brain regions at the time they process that type of information.

Third, factors that influence the contribution of particular neural systems to cognitive tasks modulate the efficiency and manner in which those tasks are performed. These include hormonal influences, eg, that increase the “tone” of some neurochemical systems, while decreasing others. Other factors, such as level of education, may serve as proxy or relatively distal expressions of the benefits to the brain of certain environmental experiences. In this context, the instantiation of learned experiences may provide alternative neural pathways to mediate the performance of cognitive tasks. This view is consistent with recent formulations of “cognitive reserve” (eg, Whalley et al, Stern et al, Pai and Tsai, Le Carret et al, Springer et al), and its consideration, in conjunction with effects of particular treatments, offers a way to conceptualize and assess the boundaries of cognitive enhancement. Fourth, the modest effects of antipsychotic medications on cognition suggest that additional psychopharmacological (and/or cognitive behavioral) interventions could add to their beneficial effects. The administration of adjunct treatments to antipsychotic medications, described above, emphasizes this point. The modest benefits of these attempts stress the early stage of the effort and the need for systematic study of potential mechanisms that could be utilized to promote memory facilitation. One such example, glucose administration, is considered next.

Glucose Administration and Memory

Overview

Effects of glucose on memory have been studied systematically for over 20 years in rodents and humans. The essential finding is that glucose, administered shortly before or after a training experience or prior to memory retrieval, improves memory for recent experiences in rodents, pigeons, and humans. Moreover, modest increases in circulating glucose improve memory in people with a variety of memory-impairing conditions such as normal aging, Alzheimer disease, Down syndrome, pretreatment with scopolamine or morphine, infantile amnesia, prenatal exposure to alcohol, and schizophrenia. The most consistently reported effect of glucose in studies with humans involves improvements in verbal declarative memory, as measured by recall of either narrative prose or a list of words. Other manipulations (eg, emotionally arousing pictures) that increase blood glucose in young subjects
also enhance recall.\textsuperscript{158,159} Several researchers noted that facilitation of memory by glucose is related to "cognitive demand", whereby greater task difficulty is associated with greater facilitation of performance.\textsuperscript{160} A number of observations are consistent with this view. First, cognitively impaired older subjects often show more improvement after glucose administration than healthy older subjects,\textsuperscript{147} and tests that are amenable to facilitation by glucose in healthy older subjects may not show any improvement in younger subjects.\textsuperscript{144–146,161} Second, the facilitation of memory by glucose administration is usually greater on delayed recall than on immediate recall in tests of verbal memory (ie, delayed recall is more difficult).\textsuperscript{162} Third, some studies report lowered peripheral blood glucose levels after a demanding task.\textsuperscript{163} Although relationships between peripheral and central glucose utilization need clarification, the finding is consistent with the view that central resources are being used in performing the cognitive task. Fourth, nonmnemonic cognitive tasks that are facilitated by glucose, such as tests of attention, tend to be cognitively demanding.\textsuperscript{160,163–166} Taken together, these results from healthy adult subjects suggest that glucose availability is most useful in facilitating declarative memory when cognitive resources are in demand. In these circumstances, the magnitude of the effect is often large (eg, \(d \geq 0.90\)).\textsuperscript{160,162,166–169} which supports its use as a heuristic intervention to reduce large (effect sizes \(\geq 0.9\)) cognitive deficits in schizophrenia.\textsuperscript{23,35}

**Glucose Regulation and Memory**

The above discussion suggests that memory performance may be related to glucose availability. Although, as noted, peripheral glucose administration is not always predictive of central glucose metabolism,\textsuperscript{145,170} there are several examples in which poor blood glucose regulation (and, presumably, availability) is related to poor memory. Among these are cognitive deficits that include verbal declarative memory in individuals with diabetes.\textsuperscript{171,172} At least some cognitive deficits, including memory, are reversed in patients with diabetes following administration of oral hypoglycemic agents and other treatments to normalize blood glucose levels.\textsuperscript{173–175} Second, glucose regulation and memory have been explored in the absence of diabetes. Several (though not all) studies involving aged subjects found that better recall of recently acquired information was associated with better glucose regulation (usually defined as the extent that blood glucose rises after an oral glucose challenge in a fasted subject, with small rises or quicker returns to baseline denoting better regulation in individual subjects).\textsuperscript{146,149,161,169,176–182} Stone et al\textsuperscript{183} obtained a parallel finding in old rats. Studies in younger subjects demonstrate more variable relationships between verbal declarative memory performance and glucose regulation than older subjects.\textsuperscript{145} They occur most reliably, however, when the task demands are relatively high for the healthy subjects.\textsuperscript{143,166,169,184} In one of these studies, glucose administration particularly improved memory in young subjects with poorer regulation.\textsuperscript{143} In another study by the same group,\textsuperscript{184} glucose administration improved memory only on the most difficult task.

**Mechanisms of Glucose Actions**

The mechanisms by which glucose modulates brain function, including memory, are multifactorial.\textsuperscript{145,185–188} Of particular importance to the current discussion is whether glucose administration and utilization modulate memory functions in ways that are direct or proximal enough to justify their exploration as treatment targets for impaired verbal declarative memory in schizophrenia. Among the reasons to question this assumption is the hypothesis that other influences, such as insulin, are either more proximal or more significant in explaining observed effects of glucose.

Glycogen storage in astrocytes, eg, is sensitive to insulin levels, possibly through modulation of glycogen synthase.\textsuperscript{189} This is potentially significant, in part, because levels of glycogenolysis in astrocytes have been shown to influence memory performance\textsuperscript{190} and also because astrocytes participate significantly in brain glucose uptake and metabolism, including glutamate-induced glycolysis and lactate production, which is transferred to neurons and oxidized via pyruvate in the tricarboxylic acid cycle to produce adenosine triphosphate (ATP) (ie, "fuel").\textsuperscript{186,187} Astrocytic glycolysis also has a stoichiometric relationship to glutamate metabolism via the glutamate-glutamine cycle, with 1 glutamate molecule cycled for each glucose molecule metabolized to lactate.\textsuperscript{186,187} Insulin may thus modulate the availability of glucose used as fuel in neurons, including the availability of glucose used for the synthesis or metabolism of neurotransmitters involved in cognition, including memory (eg, glutamate, \(\gamma\)-aminobutyric acid).

Moreover, insulin administration itself may enhance memory (eg, Watson and Craft,\textsuperscript{188} Benedict et al,\textsuperscript{191} Craft et al,\textsuperscript{192} Kern et al\textsuperscript{193}). Craft et al\textsuperscript{192} also demonstrated that insulin improved memory when glucose levels were kept constant at euglycemic levels through clamping procedures. It is important to note, however, that Craft et al\textsuperscript{192} did administer glucose to keep glycemic levels constant and that other findings show improved memory after administration of glucose or glucose analogs in the absence of increases in blood glucose.\textsuperscript{145,185,194}

These findings show that parsing out the biological effects of glucose from those of insulin is often difficult due to multiple levels of interaction. Nevertheless, the modulation of memory or other aspects of brain function by insulin does not, by itself, support the conclusion that glucose effects may be explained as functions of insulin. In contrast, multiple studies show that glucose has direct
effects in brain that are related to memory modulation, including paradigms in which microinjections of glucose or its metabolites were made into specific brain regions in animals and performance measured on specific tasks.\textsuperscript{185} Some of these studies showed that these microinjections improved memory by modulating neuronal excitability in specific regions by regulating ATP-sensitive potassium channels.\textsuperscript{195,196} Moreover, some factors that facilitate glucose effects (and improve memory), such as epinephrine administration, inhibit insulin. Other catecholamines, such as norepinephrine, have similar effects and also decrease astrocytic glycogen while increasing intracellular glucose and lactate levels.\textsuperscript{186} Finally, brain glucose uptake and metabolism are largely insulin-independent processes in humans,\textsuperscript{197} despite exceptions.\textsuperscript{189} Taken together, these findings support the view that glucose effects on memory are best conceptualized at this point in terms of their direct effects on brain function, rather than by the actions of insulin.

**Glucose, Declarative Memory, and Medial Temporal Lobe Function**

The literature on glucose effects on memory supports the following generalizations: (1) glucose improves verbal declarative memory in a variety of conditions and paradigms; (2) glucose is more effective when the task is difficult or demanding, which may mean that it is most effective when brain regions that process declarative memory are active; (3) poor glucose availability to relevant brain regions is associated with poor memory; and (4) additional glucose administration near the time of memory processing (eg, encoding or retrieval) may compensate for poor glucose availability in memory-impaired subjects or enhance processing ability in normal subjects.

The effect of glucose on memory is part of a broader spectrum of effects it exerts on brain and behavioral functions.\textsuperscript{142} Converging evidence across methodologies and species show that the medial temporal lobe, which is strongly involved in declarative memory,\textsuperscript{14,78} is particularly sensitive to glucose administration during learning and memory, especially in the presence of deficits in declarative memory performance.\textsuperscript{152,198–201} Although the findings do not identify the mechanisms by which the facilitation occurs, they are consistent with recent studies in rats showing that selective reductions in extracellular hippocampal glucose concentrations varied with the cognitive demand associated with different spatial memory tasks.\textsuperscript{170} The presence of these local decreases provides evidence that extracellular glucose is relatively compartmentalized and that greater demand during memory processing (presumably with more difficult tasks creating greater demand) produces a local extracellular glucose deficit that may be attenuated with glucose administration.\textsuperscript{170} It is particularly relevant that deficits in local glucose concentrations are greater and longer lasting under some conditions associated with poor memory, such as aging.\textsuperscript{200} The ability of glucose to improve memory under these circumstances may thus reflect its ability to reverse local deficits caused by cognitive activity involving the hippocampal and parahippocampal regions. It is of interest that intraseptal infusions of a drug (morphine) that impairs memory performance on a hippocampal-dependent task also prevents extracellular glucose reductions.\textsuperscript{201} Coadministration of glucose plus morphine both attenuates the memory deficit and results in reduced extracellular glucose levels. These findings raise the possibility of extracellular glucose levels as a marker of hippocampal function during learning.

**A Model of Vulnerability to Memory Dysfunction in Schizophrenia**

**Glycemic Dyscontrol in Schizophrenia**

The foregoing discussion provides evidence that poor glucose regulation or availability is associated with poor memory performance in a number of circumstances in rodents and humans. This raises the question of whether it is disturbed or vulnerable in schizophrenia. Several converging lines of evidence support this possibility, including (1) reports of impaired glucose regulation prior to the introduction of antipsychotic medications,\textsuperscript{202} and later, in unmedicated patients,\textsuperscript{203} patients treated with typical neuroleptic medications,\textsuperscript{204} and patients treated with newer antipsychotics\textsuperscript{205–208}; (2) recent reports of elevated levels of diabetes in schizophrenia, compared with the general population (eg, Mukherjee et al,\textsuperscript{209} Subramaniam et al\textsuperscript{210}), and impaired glucose regulation during first-episode psychosis in drug-naïve patients\textsuperscript{211}; (3) elevated rates of type 1\textsuperscript{212,213} and type 2\textsuperscript{209,214} diabetes in the relatives of patients with schizophrenia; (4) an analysis from our laboratory showing evidence of genetic linkage between 3 regulatory enzymes involved in glycolysis and schizophrenia, including 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFKFB2; chromosome 1q32.2), hexokinase 3 (HK3; chromosome 5q35.3), and pyruvate kinase 3 (PK3; chromosome 15q23)\textsuperscript{215}; (5) an exaggerated glucose response to a metabolic challenge of 2-deoxyglucose in schizophrenia\textsuperscript{a}; (6) common prepregnancy or pregnancy risk factors (including maternal diabetes) for schizophrenia and diabetes conditions\textsuperscript{217–219}; (7) similarities in the multifactorial, polygenetic nature of schizophrenia and diabetes\textsuperscript{220–224}; and (8) enhancement of verbal declarative memory in individuals with schizophrenia.

At least 3 published studies have thus far demonstrated enhanced memory performance in subjects with schizophrenia. Newcomer et al\textsuperscript{a} showed that an oral dose of glucose improved verbal declarative memory in a group of patients with schizophrenia but not in a group with bipolar disorder or in a healthy control group. The
same group also reported improvements in spatial memory and processing speed in older (but not younger) patients. In both studies, subjects were stabilized on a variety of different antipsychotic medications. In the third study, we showed that glucose improved retention for a list of words in chronic patients who were stabilized clinically on clozapine (and in most cases, additional medications). Consistent with these findings, we demonstrated that the same dose of glucose that improved retention for the list of words also activated specific brain regions (e.g., the left parahippocampus) during a verbal encoding task in a functional magnetic resonance imaging task (fMRI), compared with saccharin administration.

While it is premature to conclude that glucose dysfunction is either necessary or sufficient to produce impaired memory in schizophrenia or that memory improvement following glucose administration implies underlying glucose dysfunction, these findings, taken together, are consistent with the hypothesis that glucose dysregulation occurs in schizophrenia and adds to the liability for memory dysfunction.

Disturbed glucose function in some patients with schizophrenia, in light of the importance of glucose regulation for cognition and brain function, also highlights a need to identify neurochemical factors that modulate glucose function. Among the most important of these are hormones/neurotransmitters that regulate glucose normally but function abnormally in schizophrenia. These include insulin/insulin resistance, cortisol, epinephrine, and norepinephrine. Because each of these hormones is disturbed in schizophrenia and influences glucose regulation and availability, it is likely that one or more of them interact with and contribute to effects attributed to glucose, as discussed above. Moreover, attention to these hormones is made more salient by numerous studies showing that each of them is related to learning and memory performance. For each of these reasons, they may contribute to and influence the “boundaries” of glucose effects.

A Model of Memory Enhancement and Hippocampal Function in Schizophrenia

As noted above, the mechanisms by which glucose facilitates hippocampal function are unclear. It is likely that multiple mechanisms are involved. For example, we and other groups have shown that glucose facilitates central cholinergic function, including hippocampal cholinergic function, during learning. It is also likely that factors that modulate glucose metabolism and function, such as insulin and cortisol, mediate its function to some extent. Wenk proposed that the role of glucose in the biosynthesis of a variety of neurotransmitters (e.g., glutamate) may be related to its positive effects on memory. Moreover, glucose interactions with dopamine may be especially relevant for understanding both cognitive and clinical aspects of schizophrenia. Nevertheless, several lines of evidence discussed above point to the likelihood that elevated rates of poor glucose regulation may contribute to poor encoding and/or retrieval on tests of memory. One important question is whether poor glucose regulation is sufficient to produce memory deficits in schizophrenia. Although relatively poorer memory is associated with relatively poorer glucose regulation in healthy young adults in some studies, it seems unlikely that the subjects would be classified as having clinically significant deficits. Even young people with diabetes usually show little evidence of memory impairment. Older diabetic individuals, however, show more reliable deficits compared with age-matched controls. These findings suggest that in the absence of other impairing factors, poor glucose regulation alone may not suffice to produce memory impairment. In schizophrenia, however, other factors may be related to poor memory.

One of these, as discussed above, involves smaller hippocampi with fewer dendritic processes that are less sensitive to experiemental stimuli that would normally produce adaptive, plastic responses (e.g., encoding or retrieving new information). Interestingly, poor glucose regulation in nondemented, nondiabetic elderly people is associated with both poor memory and with smaller hippocampal volumes. In this context, lowered glucose availability, combined with a smaller, relatively inefficient hippocampus to utilize the glucose when it is available, may create or exacerbate local glucose deficits during the relatively extended periods of demand that coincide with inefficient learning (e.g., slow learning) or retrieval. A representation of this view is illustrated in figure 1. We hypothesize that a normal hippocampus is stimulated to respond adequately by an appropriate cognitive demand, which leads to efficient learning. Extracellular glucose (GLU) is utilized by the hippocampus in the process, which results in a somewhat depleted store. The depletion increases sensitivity to glucose administration, which reverses the depletion, facilitates hippocampal function, and contributes to cognitive enhancement.

In schizophrenia, we hypothesize that a smaller hippocampus that is “sluggish” or difficult to recruit will also be less efficient when it is recruited, which results in inefficient learning and ultimately a larger expenditure of glucose. This results in a larger extracellular glucose deficit and a correspondingly greater relative sensitivity to exogenous glucose administration. This view is consistent with observations from our laboratory and others showing that reduced performance of schizophrenic patients and their first-degree relatives on working memory tasks is associated with exaggerated activation in several regions, including the prefrontal cortex. In this model, Heckers’ demonstration of poor hippocampal recruitment after encoding may reflect both
a cause and/or an effect of poor hippocampal function; eg, prefrontal input may be impaired while the threshold for stimulation in an inefficient hippocampus may be higher than normal. If this view of the hippocampus in schizophrenia is correct, then abnormal hippocampal function could thus express itself through either less task-dependent activation than normal (eg, hippocampal inputs or recruitment did not rise to abnormally high threshold levels in a consistent manner) or through more activity-dependent activation than normal (eg, once a higher threshold for activity is met, greater than normal, but less regulated, levels of activity ensue). Either instance, however, is associated with inefficient learning and memory and with a partially reversible deficit in glucose availability.

Interestingly, positron emission tomography (PET) studies provide evidence that is consistent with the possibility that glucose uptake and/or metabolism may be altered in schizophrenia. One difference is that global decreases in uptake and metabolism have not been reported, to our knowledge, as they have been in diabetes. Consistent with the hypothesis of impaired regulation, however, are reports of both increased and decreased metabolic rates for glucose in different brain regions, including decreased rates in the mediodorsal nucleus of the thalamus and in temporal regions during verbal learning tasks.

**Summary and Conclusions**

This postulation of cognitive dysfunction and enhancement involving glucose regulation and administration is useful because it provides evidence that a simple intervention can serve as a heuristic model for improving memory and brain function in schizophrenia. Its emphasis here illustrates the potential value of focusing cognitive enhancement efforts on specific cognitive impairments in schizophrenia to facilitate advances in those areas, beyond levels that are likely to be associated with antipsychotic medications alone in the foreseeable future. The model also emphasizes the importance of translational research in developing and testing hypotheses and in identifying brain mechanisms involved in cognition that also map onto the neuropathology of schizophrenia.

Because no standard treatments for memory dysfunction have yet emerged, many unanswered questions remain. One that derives directly from the glucose model is whether factors that regulate or modulate glucose function, such as insulin, also enhance declarative memory. More generally, basic issues concern how and whether pharmacological interventions for memory (or other cognitive abilities) interact with specific antipsychotic medications and/or cognitive behavioral strategies to produce optimal levels of enhancement. It is likely that glucose administration itself, or other interventions that may cause or add to medication-induced hyperglycemia, will not be suitable as clinical treatments. Progress in the near future is likely to come from multiple sources, including attempts to translate findings in rodents or other nonhuman species to humans, using fMRI, PET scans, and other forms of neuroimaging. Glucose availability during learning in humans, eg, might be controlled with insulin-clamping procedures and assessed with hippocampal fMRI. Efforts aimed at increasing astrocytic glycogen storage, which would allow a larger supply of glucose in response to activity-dependent demands, along with other strategies aimed at improving glucose...
regulation in schizophrenia, offer encouraging avenues for exploration.

The robust nature of problems in learning and memory in schizophrenia raise basic questions about the efficacy of synaptic plasticity in schizophrenia and genetic and epigenetic mechanisms that control levels of plasticity. At some point, it will be important—and feasible—to link models of declarative memory dysfunction (and its potential treatments) to deficits in short-term forms of plasticity such as sensory gating paradigms (eg, p50 and prepulse inhibition) in addition to the longer term forms of plasticity inherent in declarative memory. Eventually, as genes involved in schizophrenia are identified (eg, Callicott et al, Blasi et al), epigenetic modification of target genes through environmental and pharmacological interventions may serve to modify gene expression and function in ways that will lead to adaptive modifications in neuronal signaling pathways and in declarative memory. Steps in this direction would include explorations of whether putative cognitive enhancers such as glucose administration increase transcription factors such as c-fos, cyclic AMP-responsive element binding protein (CREB), or brain-derived neurotrophic factor (BDNF) and alter gene expression in schizophrenia.

Cognitive enhancement in schizophrenia is at an early stage. However, interest in the field has increased greatly, and together with increased utilization of conceptual models to understand the nature, possibilities, and limits of cognitive improvement, better cognitive outcomes in schizophrenia are becoming increasingly more likely.

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