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Glucose improvement of memory: a review

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Abstract

The memory-improving action of glucose has now been studied for almost 20 years and the study of this phenomenon has led to a number of important developments in the understanding of memory, brain physiology and pathological consequences of impaired glucose tolerance.

Glucose improvement of memory appears to involve two optimal doses in animals (100 mg/kg and 2 g/kg) that may correspond to two physiological mechanisms underlying glucose effects on memory. In humans, there have been few dose–response studies so the existence of more than one effective dose in humans is uncertain. Many tasks are facilitated by glucose in humans but tasks that are difficult to master or involve divided attention are improved more readily that easier tasks. There are a number of hypotheses about the physiological bases of the memory-improving action of glucose. Peripheral glucose injections could alleviate localized deficits in extracellular glucose in the hippocampus. These localized deficits may be due to changes in glucose transporters in that structure. Because certain neurotransmitters such as acetylcholine are directly dependent on the glucose supply for their synthesis, glucose is thought to facilitate neurotransmitter synthesis under certain circumstances. However, these hypotheses cannot account for the specificity of the dose–response effect of glucose. A number of peripheral mechanisms have been proposed, including the possibility that glucose-sensitive neurons in the brain or in the periphery may serve as glucose sensors and eventually produce neural changes that would facilitate memory processing. These latter results could be of importance because the mechanisms they suggest appear to be dose-dependent, a crucial characteristic to explain the dose-dependent effects of glucose. There may be an advantage to develop hypotheses that include both peripheral and central actions of glucose. There is evidence that impaired glucose regulation is associated with impaired cognition, particularly episodic memory. This impairment is minimal in young people but increases in older people (65 years and over) where it may compound other aging processes leading to reduced brain function. A small number of studies showed that glucose improvement of memory is associated with poor glucose regulation although this may not be the case for diabetic patients. Results of a few studies also suggest that drug treatments that improve glucose regulation also produce cognitive improvement in diabetic patients.

Keywords: Glucose; Insulin; Glucose transporter; Memory; Attention; Aging; Diabetes; Glucose tolerance; Vagus

1. Introduction

The memory-improving action of glucose has now been studied for almost 20 years. There have been a number of important developments in the understanding of memory, brain physiology and pathological consequences of impaired glucose tolerance. The memory-improving effect of glucose on memory was originally discovered by Lapp (1981) in young high school students. She showed that giving a mixture containing 450-g carbohydrate over a 1-h period improved word learning of high school students. This effect of glucose was later rediscovered in animals by two groups (Gold, 1986; Messier and White, 1984). This memory effect of ingesting substances that increased blood glucose was also indirectly tested in two earlier studies showing that post-training food ingestion retroactively enhanced learning in mice (Huston et al., 1974; Jaffard et al., 1974). These early animal studies demonstrated that the post-training ingestion of food or glucose solutions or the injection of glucose could retroactively and non-contingently improve memory for a learned association.

At the time, this effect was interpreted in the context of early theories of learning that suggested that reinforcement could affect behavior by strengthening associations (Thorndike, 1933). Thorndike suggested that behaviors that were followed by satisfaction (reward) were more firmly associated with stimuli in the reinforcement situ-

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ation. A series of experiments by White (1989, 1991) supported his view that reinforcers (i.e. events that change behavior) have two attributes: they induce affective changes (either rewarding or aversive) and they also produce changes that facilitate memory storage.

According to this theoretical framework, glucose solutions are reinforcers because drinking them is pleasurable and they also improve memory. Separation of these two properties was made evident by the fact that saccharin solutions that were found to be equally preferred to glucose solutions (i.e. they were equally pleasurable) did not produced the same memory-improving effects (Messier and White, 1984) and that injections of glucose which do not produce taste stimulation but provide the same amount of glucose as drinking sucrose solutions produced memory improvement (Messier and White, 1987). These results suggested that some post-ingestion events were mediating the memory-improving effect of sugars while gustatory effects of the saccharin or sugar solutions mediated the affective qualities of these substances.

Although this distinction is useful for the general understanding of reinforcers' action, some results suggest that this distinction may not be absolute. In the original comparison of the effect of saccharin and sucrose solutions on memory, the animals were trained in a conditioned emotional response paradigm, in which a tone previously paired with an electric shock later produced inhibition of drinking in thirsty rats. When rats drank solutions of 4% sucrose after pairing of the tone and the shock, they remembered this association better. When rats drank a 0.5% saccharin solution, but not a 0.8% solution, a slight effect on memory was observed which was different from the absence of reinforcement but not significantly different from the effect of drinking water. Another series of experiments demonstrated that post-training ingestion of a rewarding 3.2% saccharin solution could retroactively improve retention of a place preference, indicating that taste stimulation was also able to produce memory improvement in the absence of immediate post-ingestion effects (Stefurak and van der Kooy, 1992). The interpretation of these findings has to take into account that a 3.2% saccharin solution produces both an extremely intense sweet sensation (for comparison, a 0.8% saccharin solution tastes as sweet as a 20% sucrose solution) and probably a bitter aftertaste that is usually reported at high saccharin concentrations.

Few studies have compared the impact on memory of drinking saccharin or aspartame solutions to that of drinking water. One experiment demonstrated that vigilance (but not memory) was improved when people were told that they were drinking glucose (whether or not they were receiving glucose), suggesting that the placebo effect could contribute to the improvement in cognition observed (Green et al., 2001). However, most of the human studies that examined the effect of glucose on memory used placebo solutions that were not readily identifiable by the subjects. In our own studies, the level of correct identification of the glucose versus the saccharin solution was close to chance levels although women typically scored higher. In addition, we compared the effect of drinking water, saccharin and glucose solutions and found that saccharin did not enhance memory compared to water (Messier et al., 1998), again suggesting that the placebo effect, if present, has limited impact when subjects are blind to the type of solution they drink.

Another alternative is that intense taste stimulation produced by these concentrated saccharin solutions may activate brain regions that modulate memory processing. One recent study showed that saccharin solutions increase activity in several cortical regions, e.g. the frontal operculum and the anterior part of the insula, the hippocampus, the parahippocampal gyrus and the superior temporal sulcus (Kobayakawa et al., 1999). In addition, stimulation of taste receptors has been shown to produce a small insulin secretion (the cephalic phase insulin release) that precedes changes associated with digestion (Bellisle et al., 1983; Louis-Sylvestre, 1987) and this insulin release could possible mediate some of the effect of saccharin. However, this effect was not found in humans who received an aspartame tablet, suggesting that the effect is only found in rats (Abdallah et al., 1997). Thus, available evidence suggests that saccharin may produce memory improvement under certain circumstances in animals, but that this does not occur in humans.

In conclusion, what we know of the effect of glucose and sugar on cognition suggests that this effect depends on physiological consequences of the ingestion of sugars rather than on the taste stimulation, suggesting that the rewarding (pleasurable) state produced by sugars does not mediate the effect of sugars on cognition.

The present review will examine a number of topics important for the understanding of the effect of sugars on memory. The first topic is a summary of the effect of sugars on memory in animal and human studies. Because excellent reviews have already been published (Benton, 2001; Gold, 1995; Messier and Gagnon, 1996; White, 1991), I will only briefly address the questions of dosage, the type of sugars that produce the effect, pre- and post-trial administration, the type of tasks performance of which is improved by sugars and the cognitive areas that are modulated in humans.

In Section 3, I will address the question of the physiological mechanisms proposed to mediate these effects. These mechanisms include the direct metabolic contribution of sugars to brain metabolism and neurotransmitter function. In Section 4, I will address possible peripheral mechanisms involving the indirect stimulation of the brain via the vagal system and other mechanisms. In the last section, I will present the hypothesis that the memory-improving action of glucose reveals and alleviates memory deficits that are a consequence of poor glucoregulation.

2. Descriptions of the memory-improving action of glucose

2.1. Dose-dependent effects

A number of animal studies have characterized the dose–response effect of glucose on memory. In general, animal studies showed facilitating effects at doses of 100 mg/kg or of 2 g/kg (White, 1991) but doses as low as 10–30 mg/kg were shown to modulate memory (Kopf and Baratti, 1996a; Rodriguez et al., 1994) as were also doses as high as 4 g/kg (Messier and Destrade, 1988). In humans, doses of 25 to 75 g have been shown to be effective, which corresponds to doses of 300 mg/kg to 1 g/kg for a 75-kg human. When we conducted a study in which human participants were given doses between 10 mg/kg and 1 g/kg, memory facilitation was observed only for the 300 mg/kg dose (Messier et al., 1998). We also found that doses of 2 g/kg produced nausea in many human subjects and thus were not studied further (Messier, unpublished results). In general, lower doses of glucose (25 g) appear to be more effective in young human adults while higher doses (50–75 g) are more often found to improve memory in older human adults.

Another point is that when a 100-g glucose load is ingested by humans, about 25–30 g is absorbed by the liver to be stored as glycogen and 70% is disposed of in other tissues under the stimulating influence of insulin (Radziuk, 1987). There is also a close correspondence between the rise in blood glucose and the rise in blood insulin following an oral glucose load (Fig. 1). Although data are scarce about a potential facilitating effect of insulin, it is nonetheless hard to dissociate the effect of glucose from that of insulin in the mediation of the memory-improving action of ingested or injected glucose. The observation that glucose injected in the brain facilitates memory (Lee et al., 1988) suggests a central action but other data also suggest a role of insulin. For example, two experiments have shown the ability of small doses of insulin (0.4–0.8 units/kg) to reverse the amnesia produced by a 2 mg/kg scopolamine injection (Blanchard and Duncan, 1997; Messier and Destrade, 1994) and intracerebroventricular injection of insulin can facilitate memory (Park et al., 2000). One obvious problem that has impeded further research is that exogenous insulin injection can reduce blood glucose and lead to hypoglycemia that is associated with impaired memory (Kopf and Baratti, 1995, 1996b; Kopf et al., 1998; Santucci et al., 1990). The only way to tease out the impact of insulin on brain function independently of glucose levels is the euglycemic or hyperglycemic clamp. The clamp procedure requires that a human (or an animal) be fitted with catheters allowing the sampling of blood glucose and the simultaneous infusion of glucose or hormones (such as insulin, glucagon or somatostatin) to manipulate blood glucose levels. The euglycemic clamp refers to the procedure in which blood glucose levels are maintained at normal fasting levels (5–6 mmol/l). The hyperglycemic clamp refers to a similar procedure where blood glucose is kept at higher levels (e.g. 10–12 mmol/l). These experiments conducted by Craft are described in this issue and have been generally interpreted as showing the implication of insulin in the

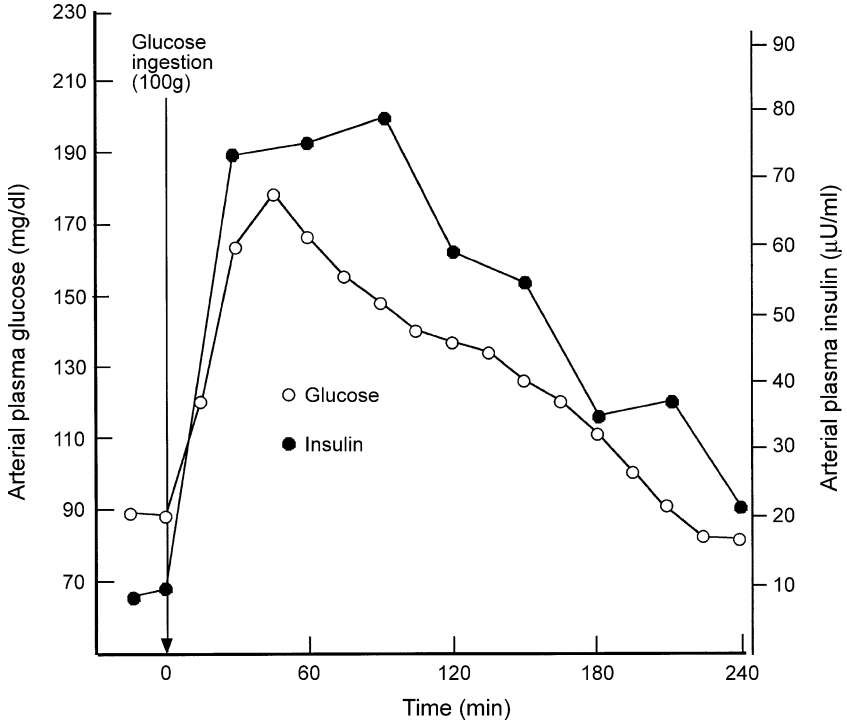

Fig. 1. Arterial blood glucose and insulin levels after the ingestion of 100 g of glucose (adapted from Radziuk, 1987).

mediation of the glucose memory improving effect. For example, raising blood insulin levels while keeping blood glucose levels constant (the euglycemic clamp) results in improved memory (Craft et al., 1999). However, in order to keep glucose levels from falling while insulin levels are raised, more glucose had to be injected so that the experiment more appropriately demonstrates that raised blood glucose is not necessary to observe memory improvement, a conclusion supported by a number of other results presented below. This type of experiment still falls short of a clear demonstration that insulin mediates the effect of glucose on memory because glucose is injected during the euglycemic clamp. Because of these difficulties, the role of insulin in cognition functions remains unclear even though insulin is implicated in other brain functions (for an extensive review, see Craft and Watson (this issue); Gerozissis, 2003).

2.2. Types of sugars that are effective

A number of different sugars have been tested for their impact on memory. In addition to glucose, fructose has been tested extensively and it was found that post-training injections of 2 g/kg fructose improved memory (Messier and White, 1987; Rodriguez et al., 1994, 1999). The lower dose of fructose (100 mg/kg) improved memory in one set of experiments (Rodriguez et al., 1994, 1999) but not in another (White, 1991). The interest in testing fructose was that this sugar is readily metabolized by the liver, does not raise blood glucose levels and does not cross the blood–brain barrier. Thus, an effect of fructose on memory would suggest a peripheral mechanism of action that could be shared with glucose. The observation by White (1991) that only the higher dose of fructose facilitated memory suggested that there were perhaps two mechanisms by which glucose improves memory: a peripheral one shared by fructose and a central one unique to glucose. However, the observation of identical dose–response curves by Rodriguez et al. (1994, 1999) suggests that this is not so. Because the tests used by White and Rodriguez were not the same, there is a possibility that the differing results for the lower dose represent differential effects on tasks that recruit different brain regions.

This hypothesis is supported by the results of Packard and White (1990) showing that different versions of a radial maze task were modulated by the different optimal glucose doses. In these latter experiments, glucose was injected following training in the maze for 5 days during which performance did not improve (on days 6 to 10, performance improved progressively). Thus in this experiment, glucose was given after the last trial where performance was at a minimum. In the first maze procedure, called win-stay, the animals had to visit four of eight arms that contained food signaled by a light. After they had obtained two food pellets in given arm, the light was turned off and no more food was given in that arm. When a 2 g/kg glucose injection (but not 100 mg/kg) was given after the end of the fifth day, it improved choice accuracy the next day and in subsequent trials (days) where no glucose was administered indicating that glucose improved memory for the association of light and food over trials 5 to 6 and that improvement facilitated further learning on the remaining days. This procedure, which does not require the animals to remember the previously visited arms but only to learn the light-food association is referred to as a reference memory task (O'Keefe and Dostrovsky, 1971), and is thought to depend on structures such as the caudate nucleus (White, 1997).

In the second procedure (win-shift), rats were first placed in the eight-arm maze with four arms blocked and food was present in the remaining four arms. After a delay, during which the animals were returned to their cages, they were again placed in the maze with the eight arms accessible and the previously blocked arms now containing food. In this procedure, the rats were trained to a criterion of four correct choices; when a rat reached criterion, it was injected with glucose immediately after reaching this criterion and tested for retention of the training 18 h later. Results showed that both the 100 mg/kg and 2 g/kg glucose dose improved the performance of the rats in this win-shift procedure. This task is thought to require the involvement of the hippocampus and is referred to as a working memory task (Olton et al., 1986; Packard et al., 1989; Packard and Teather, 1997).

Thus, these results would suggest that the low and high optimal doses of glucose improve memory that depends on the hippocampus while the higher optimal dose is specific for memory that depends on the striatum. One limitation of these data is that only few glucose doses were tested, which leaves the possibility that different tasks would show different dose–response relationships with glucose so that the effect of the higher or lower doses of glucose would have remained undetected.

In summary, the issue of whether the observations with fructose and the differential effects of glucose doses in two very similar tasks reveal two mechanisms of action or if whether the differences are due to dose–response effects remains open. This issue could easily be addressed by testing a wide range of glucose and fructose doses on a few different tasks such as inhibitory avoidance, spontaneous alternation and radial maze tasks.

2.3. Pre- and post-trial effects

One of the main differences between animal and human studies of the effect of glucose on memory is that most animal experiments used post-training glucose injections. Post-training administration of glucose is thought to reflect an action of glucose on memory processes that take place after learning about a new task or a new situation. On the other hand, pre-training glucose administration could possibly interact with attentional, perceptual and other cognitive processes taking place during and after a new learning experience. This issue was resolved for humans by an

experiment by Gold who demonstrated that both pre- and post-training administration of glucose improved memory for a paragraph recall task (Manning et al., 1992).

2.4. Tasks that are facilitated by glucose in animals

In general, most memory tasks that have been used to test memory are improved by glucose and the data pertaining to these results have been reviewed extensively elsewhere (Gold, 1995; White, 1991). Glucose effects have been demonstrated in rats as young as 17 days (Flint and Riccio, 1997, 1999) and in several species including mice, rats and pigeons (Parkes and White, 2000). Effects are observable for appetitive or aversive tasks and also for tasks where spontaneous exploration is used as the motivator (Hughes, 2002, 2003; Hughes and Neeson, 2003; Messier, 1997). However, a number of studies have also failed to demonstrate the effect of glucose on memory (Means and Edmonds, 1998; Means et al., 1996; Messier, 1998).

In one experiment, Sprague–Dawley rats were trained in a water maze alternation task and were injected 30 min before training with 1, 2 or 4 g/kg glucose (Means and Edmonds, 1998). Results indicated that glucose failed to improve learning. However glucose (at doses of 1, 2 and 4 mg/kg) attenuated (slightly) the performance deficits produced by a concomitant 0.5 mg/kg scopolamine injection but not those produced by a 5 mg/kg morphine injection. In this experiment, blood glucose levels were measured after each dose of glucose and the results indicated that the rats had an excellent glucose tolerance with blood glucose levels returning to baseline 1 h after injection of 4 g/kg glucose (the equivalent of the ingestion of 280 g of glucose in a 70-kg human). Means and Edmonds (1998) concluded that the effect of glucose may be specific to tasks rapidly learned such as inhibitory avoidance, spontaneous alternation and win-stay tasks. However, other studies have shown the effect of glucose in a win-shift task or in appetitive bar-pressing task.

In another experiment, no effect of glucose (doses ranging from 10 to 500 mg/kg) was found in young Long–Evans rats when it was injected before an appetitive delayed matching to sample task. In these experiments, performing the task at low (2 °C) ambient temperature impaired performance at all delays but glucose attenuated this impairment at short but not long delays (Ahlers et al., 1993). Because decreased performance at long delays is observed in animals with hippocampal damage (Winocur, 1991), the attenuation by glucose of the impairment produced by low temperature does not support an action of glucose on the hippocampus in this situation. However, the lack of effect of glucose in young rats in a similar delayed matching to sample task was reported at short and long intervals (Winocur, 1995).

Long et al. (1992) compared the effect of pre-trial glucose on performance in the 14-arm Stone maze of young or old (24–26 months) F-344 rats and found that glucose did not improve acquisition of this shock-motivated maze. When glucose (500 mg/kg) was administered after the third day of training (partial learning), no beneficial effect of glucose was observed the next day. A number of correlations were performed between the results of a glucose tolerance test and the number of errors in the maze. Higher peak blood glucose and insulin in the tolerance test (indicating poorer glucose tolerance) were associated with poorer performance in the maze (Long et al., 1992).

Finally, in one series of experiments, we could not replicate the memory-improving action of glucose in a strain of mice (Balb/cJ) that otherwise demonstrated normal learning abilities (Messier, 1998) even though we observed the memory-improving effect of glucose in a related strain (Balb/cByJ) (Messier and Destrade, 1988). The glucose-unresponsive strain had much lower blood glucose levels after a glucose injection, suggesting better glucoregulation. Another characteristic of this strain was a high resistance to the amnestic effects of scopolamine. One of the conclusions from these experiments was that glucoregulation somehow has an impact on cholinergic neurotransmission in the brain and that good glucoregulation was associated with no beneficial effect of glucose on memory and no impairing effects of scopolamine on memory. Conversely, poor glucoregulation was associated with memory improvement by glucose and susceptibility to the impairing effects of scopolamine. Although this hypothesis remains to be fully tested, there are indications that the memory-improving action of glucose may be more difficult to detect in animals and humans with good glucose regulation.

2.5. Human tasks that are facilitated by glucose

Although tests that measure episodic memory have been most commonly used in studies that examined the glucose effect on memory, a number of studies have found that glucose improves memory for movements (Scholey and Fowles, 2002), visual memory for drawings (Sunram-Lea et al., 2001) or faces (Metzger, 2000). Faster reaction times and better performance in a target detection task were found in children given 25 g glucose (Benton, 1990; Benton et al., 1987). Previous reviews have described the various effects of glucose on human performance (Benton, 2001; Korol and Gold, 1998; Messier and Gagnon, 1996). Instead of this, in the next sections, I will address various issues that may help understand the variability observed in human studies.

2.6. Influence of task difficulty and divided attention

As discussed below, one of the common observations is that the effect of glucose on cognition is more readily observable in older than in younger people. Because young participants are usually psychology undergraduate students who would be expected to have a good memory, one of the likely interpretations of the small effect of glucose in young people is the presence of a ceiling effect. Consequently,

several experiments have examined the impact of task difficulty on the effect of glucose on cognition.

For example, ingestion of glucose facilitated the performance of the serial sevens task during which participants have to subtract 7 from 100, then subtract 7 from the result and so on (Kennedy and Scholey, 2000). However, glucose did not improve the easier serial threes task. Similarly, glucose facilitated a fluency task in which participants had to generate as many words as possible starting with three letters with a low occurrence at the beginning of a word (Donohoe and Benton, 1999a). Glucose had no effect when the three letters began words with a higher occurrence. Glucose also improved the difficult versions of Porteus mazes but not the easy ones (Donohoe and Benton, 1999b).

Another series of experiments examined the impact of glucose when participants had to perform two tasks simultaneously. For example, in one study, participants who received either glucose (25 g) or aspartame were tested under four conditions. For the first condition, subjects had to perform a motor sequence with their hand during the presentation of a 20-word list. They also had to keep track of the number of words so that they could alternate every five words between two motor sequences. Another group of subjects had to type a four-letter sequence on a computer keyboard. Finally, an additional group of subjects was presented with a 20-word target list (California Verbal Learning Test) by a male voice and 20 distractor words were presented by female voice (Sunram-Lea et al., 2002). Results showed that the interference tasks, particularly the hand and keyboard tasks, interfered significantly with performance and that glucose attenuated these deficits, particularly the verbal list learning task, and serial sevens task.

Another experiment compared the effect of glucose (25 g), saccharin and water. Participants had to learn two lists of words, one of which was presented while they performed hand movements (fist, chop, slap) and the sequence of hand movements changed every fifth word. The glucose group remembered the word list better at the immediate and delayed free recall but no effect of glucose was found for the list when no motor interference was present. Interestingly, recognition performance for both lists was equally good in all groups, possibly indicating that memory storage as such was unaffected by glucose but that glucose only improved free recall performance under the interference condition (Foster et al., 1998).

These results suggest that the level of difficulty and the presence of interference increase the likelihood of observing the effect of glucose on cognition in young people. However, results of other experiments do not support this interpretation. For example, no differential effect of glucose was found when university students had to remember high-imagery words versus the more difficult low-imagery words (Messier et al., 1999) (but glucose did facilitate the memory for the order of words in a list, a task that is quite difficult (Awad et al., 2002)). Similarly, no effect of glucose was found in old (72 years and over) participants in the Brown Peterson, a divided attention task that requires participants to remember triads of letters while performing a serial subtraction task (Messier et al., 2003).

In conclusion, glucose appears to have a greater effect on cognition when task difficulty is increased or when attention is divided between two tasks. Additional experiments during which the nature and conditions of interference are varied systematically may better define this interaction between the effect of glucose on cognition and testing conditions.

2.7. Effects of mental effort on blood glucose

Most experiments on the impact of glucose on memory are based on the premise that glucose is the main fuel of the brain and thus increased availability of glucose through ingestion should facilitate mental processes. This is an oversimplification of the relationship between circulating blood glucose and the availability of glucose to the brain. As discussed below, at normal blood glucose, there is no overall deficit in glucose supply to the brain, even though some brain regions may experience a glucose "shortage" under some conditions (McNay and Gold, 2002). The following experiments examined the effect of mental activity on blood glucose and found a small but detectable change in blood glucose following the performance of certain tasks.

In one experiment, participants received either 25 g glucose or 30 mg saccharin and were tested on two occasions after an overnight fast during the 09:00–13:00 period (Scholey et al., 2001). They ingested the drink, studied a word list for 5 min, sat quietly for 40 min and then performed a computerized version of serial-sevens task for 5 min (they had to enter their responses on a numeric keypad and press enter. The control task was to press 555 every 3 s on a keyboard (about the rate of the other task). Blood glucose levels of about 6 mmol/l were found at 45 min. Five minutes later, the levels declined by about 0.8 mmol/l in subjects receiving glucose (five more minutes later, it declined another 0.3 mmol/l) and by 0.3 mmol/l in those receiving saccharin and stayed relatively stable. There was an improvement in serial seven performance. Blood glucose fell more after 5 min of serial sevens than after 5 min of a keyboard tapping control task, suggesting that the cognitive demand of the task produced the faster reduction (about 0.3 mmol/l in the saccharin condition and somewhat over 0.4 mmol/l in the glucose condition. A similar decline has been shown after a detection task (Donohoe and Benton, 1999b).

In this latter experiment, university students received either a placebo (aspartame/saccharin) or a glucose drink (50 g) and performed a task in which they had to detect series of three odd or three even numbers within a list of numbers (Donohoe and Benton, 1999b). Control participants just sat and did nothing in particular. Twenty minutes after drinking the solutions, participants were presented with 15 words with immediate and delayed (10 min) recalls. Participants were not fasted and ate their normal breakfast.

Overall, participants in the glucose and placebo groups performing the demanding task had a higher blood glucose (+0.8 mmol/l) than did participants in the no demand group at 20 min. Glucose did not significantly improve word recall performance but the subjects undertaking the detection task recalled more words than did those who sat quietly. Those subjects in whom blood glucose was falling and who did the detection task and received glucose remembered more words. Because initial blood glucose was not measured, it is not clear what was happening here. The fall in blood glucose at 20 min following a 50-g glucose load is puzzling because blood glucose is generally still elevated at 30-min post-ingestion. It is possible that in those subjects where glucose returned more quickly to basal levels, insulin secretion was greater and more efficient to decrease blood glucose, indicating better glucose regulation. Subjects receiving glucose did not make more correct responses than those with the placebo but tended to make fewer errors. Those subjects receiving glucose in whom blood glucose was falling at 20 min made fewer errors in a few of the trials but, again, did not make more correct responses.

It was suggested that the decline in blood glucose observed following a cognitively demanding task is due to the increased glucose uptake by the brain, leading to reduced glucose levels in the peripheral blood circulation (Donohoe and Benton, 2000). This hypothesis is weakened by a number of observations. The first one is that even though brain glucose uptake increases during cognitive tasks, the increase specific to the cognitive task performed is likely to be only a small fraction of the overall brain glucose uptake. Secondly, blood glucose levels are tightly controlled, with glucose utilization being closely matched by glucose production. For example, during sleep, there is a large (25%) decrease in brain glucose metabolism that is closely matched by decreases in glucose production while blood glucose levels remain essentially unchanged (Boyle et al., 1994). Thus, it appears unlikely that the blood glucose changes observed during and after a difficult cognitive task are due to increased brain glucose uptake. On the other hand, there are a number of studies showing that emotions, including those produced by a difficult task, lead to autonomic changes including variations in blood glucose.

2.8. The interaction of arousal and glucose and memory

In one study, students received either a 25-g glucose or a saccharin drink and performed the serial sevens, serial threes and a word fluency task and a control task (counting up from 900 by one number increment) (Kennedy and Scholey, 2000). Heart rate increased during the different tasks but the serial threes and sevens generated the highest heart rate increase. Heart rate was slightly higher in all tests during the glucose condition (around 3–4 beats/min higher for an average of 80 beats/min). Glucose improved the serial seven performance but not the word retrieval or serial threes. People with a lower baseline heart rate performed better in the serial seven and serial three tasks but not in the word fluency task.

These results suggest that people with a better performance may be less stressed and show less arousal because they mastered the task. On the other hand, if the task is impossible to master, there could be an increase in stress levels and physiological arousal that may translate as autonomic activation. This hypothesis is supported by results of a number of experiments that have specifically examined the impact of stress and stress hormones on human memory.

Parent et al. (1999) showed that the emotional arousal produced by pictures and narrative improves memory, particularly in fasted subjects receiving a placebo drink. Emotional arousal was accompanied by increased blood glucose (+6%) in the saccharin group but not the glucose group. Glucose (50 g) did not result in better memory and the effect of arousal was also less apparent in the group that received glucose. In a subsequent study that examined the impact of emotionally arousing pictures on blood glucose, a 6% blood glucose increase was observed during the test and it was concurrently associated with improved retention of the content of the pictures (Blake et al., 2001).

A number of experiments support the idea that arousal, and hormonal changes associated with it, can promote memory. For example, post-learning injection of epinephrine (120 or 240 ng/kg) enhanced the recall of visual material (Cahill and Alkire, 2003). A subsequent experiment demonstrated that a cold pressor stress (that increased cortisol levels) administered after viewing pictures improved the recall of emotionally arousing pictures but not of more neutral pictures (Cahill et al., 2003). Similarly, pre-learning cortisol administration also improved the recall of arousing pictures (Buchanan and Lovallo, 2001).

Animal experiments had previously shown that exogenous epinephrine treatment interacted with the endogenous epinephrine secretion produced by an aversive task. Memory for an aversive task with a low-intensity footshock (that produces a small release of endogenous epinephrine) is enhanced by a peripheral epinephrine injection. The same epinephrine injection impaired retention of the task when a higher intensity footshock was used (that produced a greater endogenous epinephrine release) (Gold and vanBuskirk, 1978). Similarly, glucose facilitated memory for an aversive task when the electric shock used to motivate the animal was of low intensity but the same glucose injection impaired memory when given to animals trained with a high-intensity shock (Gold et al., 1986). In a parallel human experiment, it was shown that glucose impaired memory for visual emotional stimuli but facilitated memory for neutral stimuli (Mohanty and Flint, 2001).

Together, these results raise the possibility that, in a learning situation where the subjects are challenged with a difficult task, stress hormones could interact with the action of glucose on memory, by either producing an additive facilitating or impairing effect on memory or contributing to increased variability because subjects do not necessarily react the same way to stressful stimuli.

2.9. Time of day differences

It is well known that glucose levels fluctuate on a 24-h cycle. In the afternoon and evening, blood glucose levels in response to a glucose load are about 1.5–0.30 mmol/l higher than during the morning (Van Cauter, 1990). In addition, when people are fasted and recumbent, there is a progressive decline in blood glucose (about 0.8 mmol/l) from 08:00 h onward, that is paralleled by a reduction of glucose production and utilization. Other evidence also suggests that insulin secretion is higher in the morning than in the evening (reviewed in Van Cauter et al., 1997). Finally, other hormones relevant for blood glucose levels (epinephrine, growth hormone and glucagon) do not show any important circadian rythmicity during daytime (Prinz et al., 1979; Tasaka et al., 1980) but cortisol which has a circadian rhythm characterized by a morning maximum and decreasing concentrations throughout the afternoon (Van Cauter and Turek, 1995) could interact with the effects of glucose on memory.

One experiment examined the effect of a glucose drink (25 g) or of aspartame on learning and memory using the CVLT, the Rey-Osterreith figure and digit span in 60 university students (Sunram-Lea et al., 2001). Glucose was given either in the morning after a 24-h fast, in the morning after a 2-h fast (with controlled breakfast) or in the afternoon after a 2-h fast with a controlled lunch content. Blood glucose after drinking glucose produced blood glucose patterns different from those observed in the morning and afternoon. This is consistent with the well-known influence of circadian rhythms on glucose regulation (Van Cauter et al., 1997). Memory facilitation was slightly better after a 2-h fast but there was little difference between morning or afternoon effects after a 2-h fast.

In the preceding section, I examined various aspects of the memory-improving action of glucose in animals and humans. Glucose improvement of memory appears to have two optimal doses in animals (100 mg/kg and 2 g/kg) that may correspond to two physiological mechanisms underlying glucose effects on memory. In humans, there have been few dose–response studies so the existence of more than one effective dose in humans is uncertain. Many tasks are facilitated by glucose in humans but tasks that are difficult to master or involve divided attention are improved more readily than easier tasks. Finally, tasks that produce autonomic arousal are more likely to show the facilitative effect of glucose.

3. Central mechanism of the effect of glucose on memory and cognition

The first hypothesis and probably the one most appealing intuitively is that ingested glucose improves memory by increasing access of glucose to the brain, glucose being the most important fuel of the brain. As we will discuss in this section, the main argument against such a hypothesis is the fact that the ingestion (or injection) of different doses of glucose can lead to equivalent blood glucose levels but that only a very narrow number of glucose doses improve memory (Messier et al., 1998; Messier and White, 1987). Before I tackle this issue, I would like to briefly review what we know about transfer of glucose from the blood to the brain.

3.1. Glucose and brain function: a summary

Glucose uptake and metabolism in the brain is apparently not as simple as was once thought and the existence of several intermediary processes between glucose transfer out of brain microvessels and its utilization by neurons has been proposed. These processes have important consequences for our understanding of a number of results that will be described below.

There is good evidence that glucose (and the energy contained within) follows at least three paths of entry into neurons. First glucose enters the brain parenchyma (the internal side of the blood–brain barrier) through the high–molecular (55 kDa) weight isoform of the GLUT1 glucose transporter (GLUT) present in the endothelial cells lining the blood vessels (Maher et al., 1993; Pardridge et al., 1990a). Within the endothelial cells, GLUT1 is asymmetrically distributed with a three- to four-fold higher abundance in the abluminal (on the brain side) surface relative to the luminal (on the blood vessel side) surface (Farrell and Pardridge, 1991; Vorbrodt et al., 1999). Lower GLUT1 density on the luminal surface is suggested to be important to keep glucose flowing into these cells by keeping the intracellular endothelial glucose concentration lower than that of blood plasma. The higher abundance of GLUT1 on the abluminal surface of the endothelial cells creates a concentration gradient that facilitates glucose flow from the blood to endothelial cells. Glucose is then transported out of the endothelial cells into the brain extracellular fluid and a substantial portion of glucose is transported from the brain extracellular fluid to astrocytes that have processes (end feet) that surround capillaries. The brain extracellular fluid-to-astrocyte transport is performed via the low-molecular weight (45 kDa) isoform of the GLUT1 transporter (Bondy et al., 1992; Maher et al., 1993).

The importance of the glial contribution is demonstrated by the facts that glial cells make up about half of the brain cells and that they have a higher rate of basal glucose utilization (20 nmol/mg/min) than do neurons (8 nmol/mg/min) (Magistretti and Pellerin, 1999). Once glucose is taken

up by astrocytes, it can be stored as glycogen (a large chain of glucose molecules) that is again broken down into glucose and then transported back into the extracellular fluid. The fact that astrocytes also have processes that cover synapses, suggests that astrocytes mediate an important part of the energy transfer from blood to neurons, particularly around synapses where most of increased energy demand produced by neuronal activation takes place (Sokoloff, 1981). The energy transfer can take the form of release of either glucose or lactate (a product of glycolysis) from the astrocyte into extracellular fluid and into neurons. The relative contribution of astrocytic lactate and glucose to the energy balance in neurons is still debated (Vannucci and Simpson, 2001). Astrocytes have a small store of glycogen but with a high turnover rate; glycogen is broken down into glucose by the stimulation of beta-adrenergic receptors (Fillenz and Lowry, 1998b; Fray et al., 1996; Magistretti and Pellerin, 1996). The astrocytic route is probably the one taken preferentially by glucose to reach neurons (Fillenz and Lowry, 1998a,b). Finally, the GLUT3 glucose transporter is specifically present on neurons and allows the transport of glucose from the extracellular fluid into neurons (see Fig. 2).

Thus, glucose provides energy to neurons either by direct transfer of glucose from blood vessels to extracellular fluid to neurons or by an intermediate transfer of glucose through astrocytes and by the metabolism of glucose into lactate in astrocytes and its transfer into neurons.

The final factor that controls glucose uptake is local cerebral blood flow. As blood flow increases, blood glucose concentrations remain high and may facilitate glucose entry into endothelial cells by keeping a high concentration gradient between the two compartments. Although many aspects of the mechanisms that tightly couple neuronal activation and local blood flow remain unclear, new evidence suggests that the tight coupling again may be mediated by astrocytes that are uniquely placed at the junction between blood vessels and synapses (Anderson and Nedergaard, 2003; Zonta et al., 2003).

From the discussion of the various aspects of glucose uptake and utilization, it would appear that most of the increase in glucose uptake during neuronal activation is related to increased synaptic function. Synapses have higher energy requirements because of the activity of ionic pumps involved in neurotransmission. In addition, several key neurotransmitters in the brain are directly dependent on exogenous glucose for their synthesis. This includes two of the main excitatory neurotransmitters in the brain, glutamate and acetylcholine as well as an inhibitory transmitter, gamma-aminobutyric acid (GABA) (Kaufman et al., 1991; Schousboe et al., 1993; Tucek and Cheng, 1974). Thus, synthesis of neurotransmitters may drive a portion of the changes in glucose uptake and utilization kinetics seen during neuronal activation.

Uptake of glucose through the glucose transporters is limited by the glycolytic enzymes, phosphofructokinase and hexokinase I, which activity is in turn increased by lowering of the cell's adenosine triphosphate (ATP) content (Erecinska and Silver, 1989). Since processing of ATP is the basis of the main cell mechanism of energy extraction, the ATP content of neurons drives the uptake of glucose, whereas low ATP levels increase the activity of phosphofructokinase and hexokinase and lead to increased glucose transport.

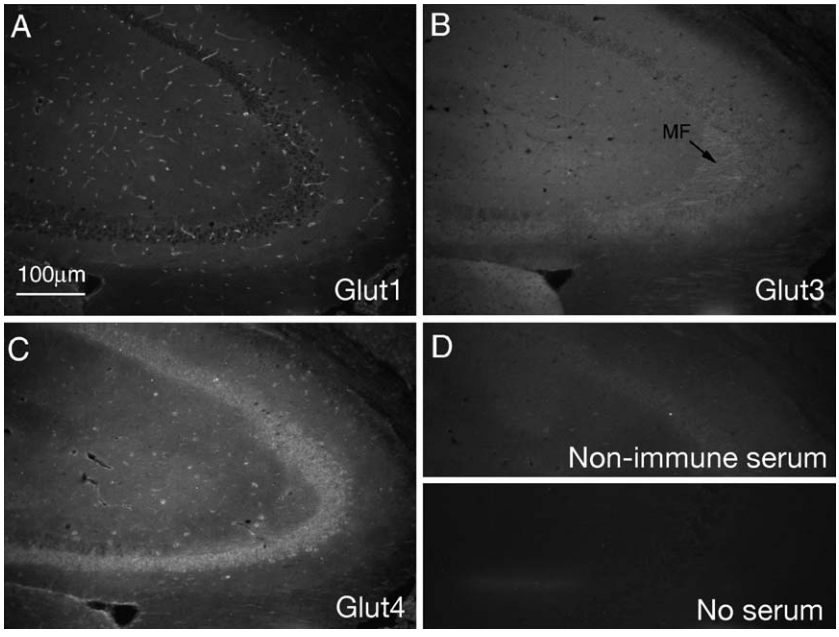

Fig. 2. Immunohistochemical localization of Glut1 (A), Glut3 (B) and Glut4 (C) or non-immune rabbit serum (D, upper half) in the CA3 region of the hippocampus. Glut3 is particularly present in the mossy fibers field of the hippocampus (arrow). The magnification bar on A applies to all four images. MF, mossy fiber field (reproduced from Choeiri, Staines and Messier, 2002).

3.2. Brain extracellular glucose levels

Although intracellular levels of glucose are tightly controlled, extracellular levels of glucose fluctuate with blood levels. The glucose content of the brain extracellular fluid has been measured in several experiments and the results vary somewhat depending on the method used, the species or the brain site from which measurements were taken. Two methods are commonly used. In vivo voltametry is performed using a glucose electrode on which glucose oxidase is immobilized on platinium electrodes. The reaction of glucose with glucose oxidase produces hydrogen peroxide that is electrically detected (O'Neil and Lowry, 2000). The other method uses microdialysis, in which a cannula with a semi-permeable membrane is implanted in the brain. A liquid (perfusate) containing various ions and glucose is circulated at the membrane level and allows exchanges between the brain's extracellular fluid and the perfusate. The perfusate is then extracted and its content analyzed (Benveniste and Huttemeier, 1990). In the case of glucose, the effect of the variation of glucose concentration in the perfusate and rate of perfusion are used to determine the extracellular fluid glucose content using the zero-net-flux technique (Lonnroth et al., 1987). In theory, these two techniques should provide very similar estimates of extracellular glucose and this has been shown in an experiment where a glucose electrode was used together with microdialysis. A value of 0.35 mmol/l (Lowry et al., 1998) was obtained which is in good agreement with the value of 0.47 mmol/l obtained using the zero-net flux microdialysis technique (Fellows et al., 1992). On the other hand, there are substantial variations between laboratories, ranging from 0.35 to 2.2 mmol/l: these variations probably represent differences in values obtained for different brain areas, from different strains of animals and animals of different age.

Experiments examining the impact of hyper- and hypoglycemia on glucose extracellular content have yielded the following results. One microdialysis experiment showed that, when blood glucose levels are normal (5.0 mmol/l) brain levels are at 1.2 mmol/l while blood levels of 17.0 mmol/l lead to brain levels of 2.4 mmol/l (Harada et al., 1993). There is a recent report on the effect of a glucose infusion on extracellular fluid glucose levels in the superior colliculus region (Jacob et al., 2002). It was found that acute hyperglycemia raised extracellular glucose from 2.1 to 8.7 mmol/l in Sprague–Dawley rats. Another study using microdialysis in human subjects undergoing surgery showed a brain glucose dialysate value of 0.82 mmol/l at normal blood glucose (5.5 mmol/l); 1.56 mmol/l at high blood glucose (11.5 mmol/l) and 0.27 mmol/l at low blood glucose (3.0 mmol/l) (Abi-Saab et al., 2002). When glucose microelectrodes were used, brain glucose levels of 2.4 mmol/l were found when blood glucose levels were normal (7.6 mmol/l) while blood glucose levels of 15.2 mmol/l led to brain levels of 4.5 mmol/l (Silver and Erecinska, 1994). Although there is a clear variation in absolute levels, what is found in general is that brain extracellular glucose levels are about 20–30% of the blood glucose levels in the physiological range.

Because brain activity is unaffected by the variation in the brain extracellular glucose levels (except in the case of extreme hypoglycemia), these results suggest that increases or reductions in brain extracellular glucose following changes in blood glucose levels are unlikely to affect overall brain function and are also unlikely to produce changes in neuronal glucose uptake because this uptake is driven by the neuron's activity, not by blood glucose concentration.

This is an important point because the effect of glucose on memory is dose-dependent, but doses of glucose that lead to identical blood glucose levels do not produce the same effect on memory in animals and humans (Messier et al., 1998; Messier and White, 1987). Thus, we can conclude that raising blood glucose levels is not sufficient to have an impact on brain function, even though brain extracellular glucose levels are increased when blood glucose is increased. In the next few paragraphs, I will describe a more localized version of the hypothesis that increased blood glucose may facilitate glucose uptake in brain regions where extracellular glucose levels are overly decreased by either high neuronal uptake or by poor transfer of glucose from endothelial cells to brain extracellular space. However, the localized version of this hypothesis still does not explain why only certain doses of glucose are effective.

3.3. The local extracellular glucose deficit

This hypothesis suggests that locally, increased glucose uptake by active neurons may lead to a local deficit in extracellular glucose, sufficient to become rate-limiting for glucose transfer from extracellular space to neurons. This possibility is suggested by the results of a series of experiments by McNay and Gold (2002).

In these experiments, the authors examined the changes in hippocampal extracellular levels during the performance of a memory task in which animals spontaneously explore a four-arm maze. Animals tend to alternate spontaneously between arms and this alternation depends on memory processes that allow the animal to remember which arms it previously visited. Drugs that impair memory reduce alternation while drugs that facilitate memory increase the alternation rate, presumably by facilitating memory storage of previously visited arms (Lalonde, 2002). Because this task relies of the use of spatial cues, it is also thought to involve the hippocampus (Johnson et al., 1977). The zero-net flux microdialysis technique was used, yielding values for resting extracellular glucose of 1.2 mmol/l in the hippocampus and 0.7 mmol/l in the striatum (McNay and Gold, 1999; McNay et al., 2001). It was found that when young Sprague–Dawley rats performed a spontaneous alternation task in a four-arm maze, there was a rapid 30% decrease in hippocampal extracellular glucose within less than 5 min after the start of the alternation task but that

glucose levels rapidly returned to their basal values at the end of behavioral testing (McNay et al., 2000, 2001). When animals received a 250 mg/kg intraperitoneal glucose injection, hippocampal extracellular glucose levels remained at basal levels. This injection of 250 mg/kg glucose increased alternation rates, suggesting that improved memory was associated with the normalization of hippocampal extracellular glucose.

In animals with a microdialysis probe in the striatum, extracellular glucose levels did not decrease in response to training but tended to increase slightly and follow blood glucose changes. Thus, these experiments demonstrated a region-specific decrease in extracellular glucose during the performance of a memory task. In one experiment, the decrease in extracellular glucose was reduced when the animals performed a three-arm alternation task, which was less difficult and presumed to require less processing (McNay et al., 2000), suggesting that task difficulty induced a larger decrease in extracellular glucose. In animals undergoing the three-arm alternation task, the hippocampal extracellular glucose decrease was minimal and injection of 250 mg/kg glucose did not increase alternation behavior.

In another experiment, the changes in hippocampal extracellular levels in young and old F-344 rats were examined during a four-arm alternation task (McNay and Gold, 2001). It was found that the alternation task was associated with a 12% decrease in hippocampal extracellular glucose levels in young rats while old rats showed a 48% decrease. The injection of 250 mg/kg glucose abolished these decreases and also increased the number of alternations, indicating better memory.

These results suggest that the hippocampal extracellular supply of glucose is decreased in older animals. Another indication that this may happen is that McNay and Gold (1999, 2001) had to reduce the flow rate of the perfusate in older F344 rats to obtain a linear response when they examined the impact of glucose concentration in the perfusate on the glucose level in the dialysate. It is unlikely that glucose demand is increased in the brain of older animals because brain glucose utilization decreases with age, including that in the hippocampus (Ebeling et al., 1998; Gage et al., 1984; Kuhl et al., 1982, 1984; Petit-Taboue et al., 1998; Tack et al., 1989). Rather, these results suggest that the efficacy of glucose transfer to the extracellular space is reduced in aging and that glucose uptake by neurons is not compensated efficiently, at least locally in the hippocampus.

3.4. The glucose transporter deficit hypothesis

We have described in the previous section how brain extracellular glucose levels follow closely blood glucose levels and remain at 20–30% of blood levels. This relation of brain to blood levels is determined by the asymmetrical distribution of GLUT1 glucose transporters in the endothelial cells lining capillaries whereas lower GLUT1 levels on the vascular side compared to the brain side of endothelial cells results in a glucose gradient that facilitate the entry of glucose into the brain. From the point of view of glucose transport, there should not be a local deficit in glucose transfer from blood to brain, because blood glucose had to be raised to normalize extracellular glucose levels in the McNay et al. (2000, 2001) experiments, their results suggests that there may be a deficit in the GLUT1 transfer of glucose from the blood to the brain with aging and that slightly increasing blood glucose levels is sufficient to overcome this deficit.

Changes in the distribution of GLUT1 have been reported in chronic hypoglycemia (induced by continuous-release insulin pellets) whereas there was a 23% increase in overall GLUT1 levels but a 52% increase of GLUT1 on the vascular side of endothelial cells (Simpson et al., 1999). These changes in GLUT1 numbers and distribution were associated with an increase in glucose uptake. These results suggest that reorganization of the distribution of GLUT1 glucose transporters can lead to changes in glucose availability. Because we observed that impaired glucose tolerance that is characterized by transient higher insulin and glucose levels was associated with impaired memory (Awad et al., 2002; Messier et al., 1997, 1999, 2003), it was interesting to see if chronic hyperglycemia results in opposite changes in GLUT1 densities. Results from studies that examined the impact of streptozotocin-induced diabetes or genetically linked diabetes on GLUT1 distribution were inconsistent with results of some studies reporting a reduction in GLUT1 transporters (Duelli et al., 2000; Gjedde and Crone, 1981; McCall, 1992; Mooradian and Morin, 1991; Pardridge et al., 1990b) while other studies did not find this (Pelligrino et al., 1992; Simpson et al., 1999). In one recent study, there was also no redistribution of GLUT1 following streptozotocin-induced hyperglycemia (Simpson et al., 1999) and no specific changes in the GLUT1 content in the hippocampus (Duelli et al., 2000; Simpson et al., 1999).

Although there have been some reports of decreased GLUT1 densities in aging animals (Gschanes et al., 2000; Vorbrodt et al., 1999), further studies are needed to examine the relative distribution of vascular/brain GLUT1 including a control for microvascular density in the aged brain. A number of experiments also remain to be done to fully test the preceding hypotheses. First, because of the inherent limitations of the zero-net-flux microdialysis method, the hippocampal extracellular glucose decrease during a memory task in both young and aged animals should be replicated with glucose electrodes, using in vivo voltametry. Secondly, a dose–response curve for the effect of glucose on hippocampal extracellular glucose decrease during a memory task should be performed to demonstrate that particular doses of glucose produce specific effects on brain glucose levels. Although quite hypothetical, one could suppose that certain patterns of blood glucose changes could be associated with specific effects on hippocampal extracellular glucose levels. Finally, the changes produced by aging in the various components of the blood–brain transfer of glucose should

be examined, including quantification of the various glucose transporters and key enzymes associated with them.

As we discussed earlier, one of the important roles of glucose in the brain is the supply of precursor for several neurotransmitters including glutamate, GABA and acetylcholine (Miccheli et al., 2003). In the search for a mechanism to explain glucose improvement of memory, much attention was given to the link between glucose and acetylcholine, evidence for which will be reviewed in the next section.

3.5. Pharmacological interaction between the effect of glucose and cholinergic drugs

A number of experiments have shown that the amnesia produced by scopolamine, a nonspecific muscarinic receptor antagonist, for many different tasks is attenuated by peripheral glucose injection (Messier et al., 1990; Stone et al., 1988b, 1991, 1992). AF-DX116, a presynaptic muscarinic receptor antagonist, potentiated the effect of glucose in Swiss mice (Kopf et al., 1998). In that experiment, post-trial injection of a dose of 0.3 mg/kg AFDX-116 that itself had no effect on the retention of an inhibitory avoidance task was combined with an equally ineffective post-training injection of 10 mg/kg glucose injection: combined injection of the two substances improved memory. AFDX-116 blocks the pre-synaptic muscarinic receptor that controls the release of acetylcholine by negative feedback: blockade of these receptors increases acetylcholine release (Lapchak et al., 1989) and improves memory (Packard et al., 1990). Similarly, it was found that the post-training injection of a suboptimal dose of glucose (10 mg/kg) together with a suboptimal dose of physostigmine (35 μg/kg) but not neostigmine (a peripherally acting anticholinesterase inhibitor) facilitated retention of the exploration of an open field (Kopf and Baratti, 1996a) and of a step-through inhibitory avoidance task (Kopf and Baratti, 1994). Similar interactions between glucose and physostygmine were found, whereas the injection of glucose increased the intensity and accelerated the onset of physostigmine-induced tremors (Stone et al., 1988a).

The interaction between cholinergic drugs and glucose was studied in Swiss mice, using the effect of post-training injections on a habituation response to exploration of a new environment (Kopf and Baratti, 1996a). When glucose (30 mg/kg) was injected after a 10-min exploration of an open field, it produced a dose-dependent significant reduction of exploration of the maze the next day, while delayed glucose injections were ineffective. This effect of glucose was abolished by the muscarinic antagonist, atropine (0.5 mg/kg), but not by the peripherally acting methylatropine. Atropine itself had no effect on the habituation response. The effect of glucose was also abolished by the nicotinic antagonist, mecamylamine (5 mg/kg), but not by the peripherally acting nicotinic antagonist hexamethonium. Similar results were obtained using a step-through inhibitory avoidance task except that the nicotinic antagonist, mecamylamine (5 mg/kg), had no effect (Kopf and Baratti, 1994). The memory-improving effect of the anticholinesterase, tacrine, was enhanced when glucose (50–100 mg/kg) was combined with lower (0.5–1 mg/kg) but not higher (2–3 mg/kg) tacrine doses (Pavone et al., 1998). Although these results can be taken as supporting the interaction between glucose and acetylcholine, one has to remember that most drugs that facilitate memory also reverse the amnestic effect of scopolamine so that the effect of glucose could be mediated by a number of other neurotransmitter systems. However, a number of experiments that measured hippocampal acetylcholine levels in animals receiving cholinergic drugs and glucose have supported an interaction between glucose availability and acetylcholine levels.

3.6. Microdialysis experiments examining the impact of glucose on acetylcholine synthesis

The interaction between glucose and cholinergic function was demonstrated in a number of studies that examined changes in cholinergic function mostly in the hippocampus. The rationale for these experiments stems from the fact that acetylcholine is synthesized from choline and acetylcoenzyme A (Tucek and Cheng, 1974; Tucek et al., 1982). In the brain, acetylcoenzyme A derives from the Krebs cycle of glucose metabolism. A number of early studies indicated that the pool of acetylcoenzyme A used to metabolize acetylcholine is compartmentalized, which means that the pool of acetylCoA used for acetylcholine synthesis appears to be different from that used for other cellular functions (Gibson and Blass, 1976; Gibson et al., 1978; Gibson and Shimada, 1980). The idea of compartmentalization is also derived from observations that cognitive processes, and particularly memory, are impaired at glucose levels higher than those producing general impairment of brain metabolic activity, suggesting that certain brain functions and areas may be more easily impaired when brain extracellular glucose levels are decreased.

A first series of experiments used muscarinic antagonists to induce uncontrolled release of acetylcholine from presynaptic neurons. This effect is due to the negative feedback loop controlled by muscarinic presynaptic receptors which modulate acetylcholine release. When these receptors are activated by the presence of high levels of acetylcholine in the synaptic cleft, acetylcholine release is reduced. Conversely, when these receptors are blocked by antagonists (mimicking low acetylcholine levels), acetylcholine is released in larger quantities and presynaptic acetylcholine content is reduced. Early experiments demonstrated that the atropine-induced decrease of presynaptic acetylcholine content in the caudate nucleus was attenuated by peripheral glucose injections whereas glucose had no effect in animals that did not receive atropine (Dolezal and Tucek, 1982). The depletion of acetylcholine content from the striatum and hippocampus (but not the cortex) produced by quinuclidinyl

benzilate, another muscarinic antagonist, was attenuated by peripheral glucose injections (Ricny et al., 1992). Another experiment showed that peripheral glucose injections (2 g/kg) increased scopolamine-induced acetylcholine release from the hippocampus (Durkin et al., 1992), suggesting that increased glucose levels facilitated acetylcholine synthesis. However, in the latter experiment scopolamine induced a 1200% increase in acetylcholine release (see Fig. 3) while glucose further increased release to 1700% of baseline (Durkin et al., 1992). Although these experiments demonstrated the facilitation of acetylcholine synthesis by glucose, they also revealed that there is ample metabolic reserve for acetylcholine synthesis and release. Additionally, it was not clear from these experiments whether the facilitating effect of glucose on acetylcholine synthesis was at all relevant for behavior-induced neuronal activation.

In a series of microdialysis experiments, Ragozzino et al. (1996) showed that peripheral glucose injections dose dependently potentiated the increase in hippocampal acetylcholine output produced when rats explored a four-arm maze. In this experiment, exploring the four-arm maze was associated with a 50% increase of acetylcholine output and peripheral glucose injection of 250 mg/kg further increased the acetylcholine output by another 50% while a 1000 mg/kg glucose injection had no effect on acetylcholine output. As in previous experiments, glucose did not produce an increase in acetylcholine output when animals were left in their home cage. Additionally, the dose of glucose (250 mg/kg) that produced the greatest increase in acetylcholine outflow was also the dose that facilitated alternation between arms of the maze, indicating that these animals better remembered the arms that the had previously entered.

A follow-up microdialysis experiment again demonstrated that the performance of spontaneous alternation in a four-arm maze was associated with a 36% increase in acetylcholine outflow from the hippocampus (Ragozzino et al., 1998). When glucose levels in the dialysate were raised from 3.3 to 6.6 mM, hippocampal acetylcholine output increased 94% and the infusion of 6.6 mM glucose was associated with an increase in alternation, suggesting improved memory processing. Again, increasing glucose levels in the dialysate did not increase acetylcholine output in animals when they were in their home cage. Additional data showed that microinjection of 6.6 mM glucose in one hippocampus produced an increase in acetylcholine output in the contralateral hippocampus. This effect is consistent with a direct or indirect connection between hippocampi (Swanson et al., 1978). Together, these experiments show that glucose can alter brain function either directly, as demonstrated by the effect on the acetylcholine outflow ipsilateral to the side receiving glucose, or indirectly by changing neural activity in one brain area (for example the hippocampus), leading to changes in other brain areas having functional connections with the hippocampus.

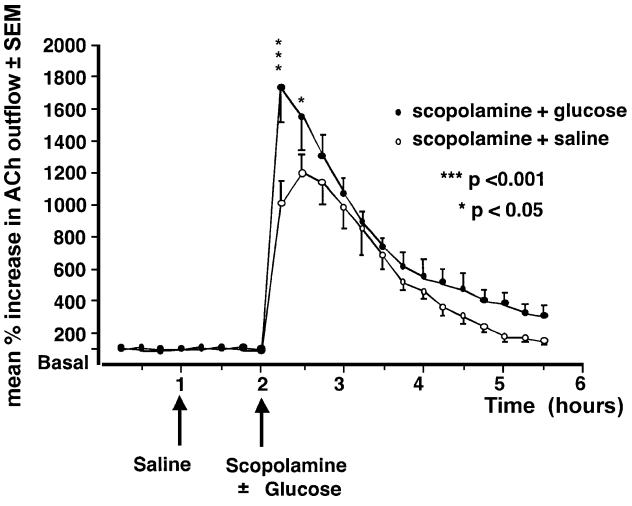

Fig. 3. Time-course of acetylcholine outflow from the hippocampus. Values are expressed as % of mean basal release ± S.E.M. Scopolamine (1 mg/kg) increased acetylcholine outflow while glucose (2 g/kg) further increased this effect (reproduced from Durkin et al., 1992).

When compared to the 1200% acetylcholine release increase produced by scopolamine, the changes produced by behavior-driven neuronal activation are quite modest. It is difficult to imagine that, in behavior-driven neuronal activation, acetylcholine synthesis is limited by acetylcoenzymeA because scopolamine was shown to drive acetylcholine release at a much higher rate, suggesting that behavior-driven neuronal activation does not deplete acetylcholine stores or metabolic compartment.

Similar experiments have also shown that much smaller doses of glucose could produce an increase in hippocampal acetylcholine output. For example, Kopf et al. (2001) examined the impact of peripheral glucose or choline on acetylcholine output in the hippocampus (Kopf et al., 2001). A first series of behavioral experiments showed that doses of 30 mg/kg glucose or 60 mg/kg choline each produced improvement for an inhibitory avoidance task. When a suboptimal dose of glucose (10 mg/kg) was combined with a suboptimal dose of choline (20 mg/kg), memory was also facilitated; however, lower or higher doses of choline were not effective when combined with 10 mg/kg glucose. When the effective dose of glucose (30 mg/kg) was combined with choline 20–60 mg/kg, it abolished the memory-improving effect of glucose. It was then shown that the combination of a suboptimal dose of glucose (10 mg/kg) with a suboptimal dose of choline (20 mg/kg) produced an increase in ACh hippocampal output when scopolamine was added to the dialysate. This same combination also potentiated the hippocampal acetylcholine output increase produced by the exploration of a novel environment. Because the 10 mg/kg dose of glucose is unlikely to have produced any elevation of blood or brain glucose concentrations these results are more consistent with a signaling function of glucose than with a metabolic impact.

Together, the results discussed above suggest that raising extracellular glucose levels in the hippocampus can increase acetylcholine synthesis through increased availability of

acetylcoenzyme A. However, this conclusion is weakened by the observation that certain glucose doses that raise blood glucose (and presumably brain extracellular glucose levels) neither improve memory nor increase acetylcholine output (Ragozzino et al., 1996). These results are incompatible with the hypothesis that raising blood glucose improves memory by increasing brain extracellular glucose levels or precursor availability for acetylcholine. In addition, as demonstrated by the large output of hippocampal acetylcholine in scopolamine-treated animals (1200% of basal levels), there appears to be a precursor pool sufficient to sustain an acetylcholine synthesis much greater than the increases (150% of basal levels) reported following behavior-driven neuronal activation.

4. Peripheral mechanisms

4.1. Contribution of the vagus nerve

As discussed earlier, a number of experiments have suggested that the primary site of action of glucose may be in the periphery. For example, glucose could act on a detection mechanism in the liver. This mechanism would then send a neural signal to the central nervous system to influence the physiological processes underlying memory formation. This hypothesis is supported by a number of observations.

Coeliac ganglion lesions that effectively block most of the efferents of the liver have been shown to abolish the effect of large doses of glucose on memory (White, 1991). This observation is consistent with the results of a number of experiments that demonstrated that vagotomy produced an attenuation of the memory-enhancing effects of several peripherally injected drugs (Flood and Morley, 1988; Flood et al., 1987; Nogueira et al., 1994; Williams and Jensen, 1991, 1993).

Secondly, stimulation of the vagus nerve has been found to either improve (Clark et al., 1999; Sackeim et al., 2001) or impair (Helmstaedter et al., 2001) cognitive functions in humans. However, interpretation of these results is difficult because they involved either epileptic or treatment-resistant depressive patients. Depressed patients typically suffer from cognitive impairments, including memory deficits that are typically alleviated by treatment. In one study, it appeared that the improvement in cognition produced by vagal stimulation was associated with the reduction of depressive symptoms (Sackeim et al., 2001), suggesting a nonspecific effect of the stimulation through the improvement of depressive symptoms. In another study, acute vagal stimulation improved verbal learning in epileptic patients (Clark et al., 1999); although there was no significant correlation between self-reported seizures and memory performance, an effect of mood improvement in these patients or other nonspecific effects of the vagal stimulation cannot be ruled out. However, vagal stimulation was also found to improve memory in rodents, suggesting that vagal stimulation can improve memory (Clark et al., 1995). The effect was current-dependent, whereas 0.4-mA stimulation improved retention, higher or lower currents did not. Additionally, in this later study, lidocaine was injected below the level where vagal stimulation was applied (thus preventing descending vagal neural stimulation from the neck down). The memory-improving effect of 0.4-mA stimulation was still found when vagal nerves were blocked. This experiment demonstrated that the effect of vagal stimulation depended on the activation of central nervous structures.

Functional neuroimaging in epileptic and depressed patients revealed that vagal stimulation produces strong activation of the thalamus and cerebellum while less consistent activation is found for the orbitofrontal cortex, anterior temporal cortex, insula and hypothalamus (Chae et al., 2003). Most vagal nerve fibers terminate in the nucleus of the tractus solitarius, and dorsal motor nucleus, and reversible inactivation of this nucleus attenuates the effect of peripherally acting substances such as epinephrine (Williams and McGaugh, 1993). Activation of the nucleus of the tractus solitarius has been shown to result in changes in the amygdala, a brain region involved in memory processing (Clayton and Williams, 2000; Miyashita and Williams, 2002; Williams et al., 2000). Together, these results suggest that changes in certain peripheral organs such as the liver could influence brain function, possibly through activation of a vagus-nucleus of the tractus solitarius-amygdala circuit.

4.2. The nature of the peripheral signal

There are data suggesting the possibility that glucose has both a peripheral (on the same physiological substrates as fructose) and a central action. The peripheral action could be initiated by a neural signal produced when glucose is carried into cells by the glucose transporter mechanisms. This hypothesis is supported by the demonstration that 3-*O*-methylglucose, a glucose analog that has the same affinity for the glucose transporter but is not metabolized once inside the cell (Jay et al., 1990; Malaisse-Lagae et al., 1986), also improves memory at the same high optimal dose as glucose but does not raise blood glucose (Messier and White, 1987). This peripheral action could conceivably involve intracellular signalling triggered by the binding of glucose or its analogs to glucose transporters situated on the membrane of glucose-sensitive cells of the peripheral nervous system (Niijima, 1989). This hypothesis is further supported by results of an experiment using phlorizin, a substance that has a high affinity for the extracellular portion of the glucose transporter but is not itself transported (Silverman, 1991).

Post-training injection of phlorizin (30 μg/kg) was found to improve the retention of an inhibitory avoidance task in Swiss mice (Boccia et al., 1999) and also improved retention when given pre-trial (3 μg/kg) in DUB-ICR mice (Hall

et al., 1992). In this latter experiment, it was found that phlorizin did not increase blood glucose nor produced changes in 2-deoxyglucose uptake in several brain regions including the hippocampus, cortex or septum even though the 2-deoxyglucose uptake following phlorizin injection tended to be lower (Hall et al., 1992), suggesting that the effect of these low doses of phlorizin on memory was independent of an action on blood glucose regulation or on brain glucose uptake. These results suggest instead that the action of phlorizin on memory on its binding its binding to the glucose transporters.

The second possible mechanism for a glucose-mediated peripheral sensor involves glucose-sensitive neurons. Glucose-sensitive neurons were originally described in the hypothalamus by Anand et al. (1964) and Oomura et al. (1964). They have since been observed in various hypothalamic nuclei, the substantia nigra, the area postrema and the nucleus of the tractus solitarius (Levin, 2002). Neurons that change their activity depending on glucose extracellular levels can either increase their firing activity with rising glucose levels (called glucose-excited by Levin, 2002) or decrease their firing activity with rising glucose levels (glucose-inhibited). Similar glucose-sensitive cells are found in the hepatic portal vein and the carotid body (Alvarez-Buylla and de Alvarez-Buylla, 1988; Hevener et al., 2000) and can detect changes in extracellular glucose as slight as 0.1–0.2 mmol (Song et al., 2001). Glucose-excited neurons are homologous to pancreatic beta-cells that release insulin. Glucose-excited neurons utilize an ATP-sensitive K+ channel (K_{ATP}) whereas an increase in extracellular glucose leads to an increase in intracellular glucose and in turn the ATP produced by glucose metabolism inactivates the K_{ATP} channel. The K_{ATP} channel is composed of a sulfonylurea receptor and a Kir6.2 pore unit through which potassium transits (Ashford et al., 1990; Liss et al., 1999; Rowe et al., 1996). In glucose-sensitive neuron and beta-cells, glucose utilization is controlled by glucokinase rather than hexokinase 1 (Matschinsky, 1990). Because the half-maximal velocity constant (K_m) is close to the physiological range of extracellular glucose concentration, glucokinase can be rate-limiting for the activation of the K_{ATP} channel.

In support of this hypothesis, the peripheral injection of minoxidil (a K_{ATP} opener) or glibenclamide (a K_{ATP} blocker) attenuated or enhanced the memory improvement produced by a 1 g/kg glucose injection (Rashidy-Pour, 2001). Another experiment showed that lemakalim (a K_{ATP} opener) reduced spontaneous alternation when injected in the hippocampus, while glibenclamide and glucose increased alternation scores (Stefani and Gold, 2001). Both lemakalin and glibenclamide increased hippocampal acetylcholine output, suggesting that increased acetylcholine release did not mediate the differential impact of the drugs on spontaneous alternation. In another experiment it was shown that glibenclamide dose-dependently improved spontaneous alternation when injected in the septum (Stefani et al., 1999). In addition, independently sub-effective doses of glibenclamide and glucose improved spontaneous alternation when injected together in the septum (Stefani et al., 1999).

Together, these results suggest the possibility that glucose-excited neurons in the brain or in the periphery may serve as glucose sensors and eventually produce neural changes that would facilitate memory processing. These results could be of importance because the mechanisms they suggest appear to be dose-dependent, a crucial characteristic to explain the dose-dependent effects of glucose. The other attractive feature of this mechanism would be that it could explain both putative peripheral and central actions of glucose. Additionally, glipizide, another sulfonylurea drug has been shown to improve verbal memory in diabetic patients (Gradman et al., 1993). This area of research is one that is still uncharted and in need of further experimentation.

The fact that the peripheral mechanisms proposed are more likely to be dose-dependent means that they could provide the missing link to central hypotheses such as the localized glucose or acetylcholine deficits. It is possible that both central and peripheral mechanisms operate to produce the optimal physiological states that will lead to memory facilitation.

4.3. Some surprising results in need of further study

A number of experiments have demonstrated that L-glucose, a stereoisomer of glucose can modulate memory. For example, working and reference memory was facilitated in C57/BL6 mice that were tested in the Morris water maze after they received an injection of 300 mg/kg L-glucose (Lawson et al., 2002). This effect was abolished by either a 0.3 mg/kg methylscopolamine or a 1 mg/kg hexamethonium injection, two peripherally acting cholinergic antagonists. Additionally, L-glucose attenuated the amnesia produced by a peripheral morphine injection as did D-glucose (Talley et al., 1999). In another experiment where Swiss mice received either 30 mg/kg D-glucose or 30 mg/kg L-glucose after training in an inhibitory avoidance task, there was a memory-improving effect of D-glucose but not of L-glucose (Kopf et al., 1998). Vagotomy blocked the improvement in spontaneous alternation produced by 3 g/kg L-glucose but not that produced by 250 mg/kg D-glucose injection suggesting that L-glucose acted through a peripheral mechanism (Talley et al., 2002).

The puzzle of L-glucose action resides in its physiological inactivity as an L-isomer. L-Glucose is transported across the membrane of isolated liver cells but at only 5% of the rate of D-glucose (Baur and Heldt, 1977). L-Glucose should be metabolically inactive and does not enter cells through the glucose transporter mechanism (Kohn and Clausen, 1971; Meyer and Scharrer, 1991; Park et al., 1968). Injection of 300 mg/kg L-glucose does not increase circulating glucose levels, demonstrating that L-glucose does not get transformed into D-glucose (Talley et al., 1999).

One possible way to investigate this puzzling issue is to examine the effects of various hexoses, for example D-galactose and its derivatives, that interact to various degrees with glucose transporters (Barnett et al., 1975).

Finally, a recent experiment compared the impact on memory of different drinks that contained the same amount of energy (774 kJ), as either glucose (50 g) protein (50.6 g whey protein), or fat (41.1 g of safflower oil emulsion) (Kaplan et al., 2001). It was found that all three solutions improved the recall of a prose paragraph as compared to a saccharin placebo. Although, in theory, protein and fat could have an action on the brain, the memory-improving effects were found 15 min but not 60 min after ingestion, suggesting that fat and protein acted on a peripheral mechanism possibly different from that used by glucose since fat and protein had no effect on blood glucose. A previous experiment that examined the impact of different carbohydrate foods showed that glucose and potatoes, that raised blood glucose to similar levels, had the same memory-improving effect as did barley, a food that produced a much smaller blood glucose increase (Kaplan et al., 2000). Together, these findings suggest that memory improvement through peripheral action is independent from blood glucose levels and that there may be a common mechanism for the action of these various nutrients on cognitive function, and also that the resulting neural signal is being transmitted through the vagus to the nucleus tractus solitarius where it may be relayed to various brain structures. Alternatively, gut hormones that are secreted in response to a meal could mediate the effect of glucose and other nutrients; cholecystokinin, (Itoh et al., 1988; Kádár et al., 1981; Telegdy et al., 1985) and bombesin (Flood and Morley, 1988; Williams and McGaugh, 1994) have been shown to improve memory when injected peripherally or into the brain ventricles, suggesting that they could mediate nutrient effects on memory.

In summary, a number of observations suggest the existence of one or more peripheral mechanisms that mediate the effects of glucose and other sugars as well as of other nutrients. Possible mechanisms include glucose-responsive neurons in the liver or elsewhere that transmit a neural message via the vagus nerve and a hormonal mediator released by the gut which could act in the periphery or centrally to influence brain activity related to memory processing.

5. The impact of peripheral glucoregulation on memory functions and its relationship to the memory-improving action of glucose

I will now consider the hypothesis that the memory-improving action of glucose is the hallmark of pre-existing memory deficits. That is, glucose improves memory in animals and humans that have memory deficits but not in animals or humans that have optimal memory processes. Secondly, I propose that one of the processes by which memory is commonly impaired is the impairment of glucose tolerance. A number of studies in animals or humans support this hypothesis, even though the mechanisms by which impairment of glucose tolerance leads to memory deficits remains unknown.

5.1. Animal studies

Feeding young rats high levels of saturated fats for 3 months, a procedure that leads to impaired glucose tolerance and reduced insulin sensitivity (Clandinin et al., 1993; Pan and Berdanier, 1991; Storlien et al., 1991), also produces memory impairments (Greenwood and Winocur, 1990, 1996; Winocur and Greenwood, 1993, 1999). In one experiment, Greenwood and Winocur (2001) examined the impact of a variable interval delayed alternation task that has been used to dissociate the effects of frontal cortex lesions from those of hippocampal lesions: In this task, rats with frontal lesions have difficulty learning the alternation response irrespective of the intertrial interval, while animals with hippocampal lesions only performed poorly at long intertrial intervals. High-fat diets produced performance deficits, particularly at longer intertrial intervals, suggesting that impaired glucose regulation and a glucose effect on cognition modulated hippocampal-dependent but not frontal cortex dependent aspects of the task. The deficits were reversed by a 100 mg/kg glucose injection (Greenwood and Winocur, 2001). Interestingly, there was no effect of glucose in animals that received normal chow even at the longer intertrial intervals suggesting that glucose was effective because of the pre-existing deficit produced by the high-fat diets.

In another experiment, older rats (Long–Evans in this case) were compared with young animals for their ability to acquire a conditioned discrimination learning in which they learned to lever press two levers to obtain food; the lever which was associated with food delivery was signaled by a light situated over each lever and a delay between light appearance and the introduction of both levers could be added (Winocur, 1995). Older animals tended to learn this task more slowly and their performance degraded rapidly as the time interval between the presentation of the light stimulus and the levers was increased. In this experiment, older animals that also presented with worse glucoregulation were impaired under the delayed conditions but their performance at longer delays improved when they received a glucose injection. Their performance in the task in the absence of delay was also worse than that of young animals but was not improved by the glucose injection. Finally, the performance of young rats was unaffected by the glucose injection.

Previous studies had shown that the acquisition and performance of this conditioned discrimination learning was impaired in animals with prefrontal cortex lesions when there was no delay between the light stimulus and the

opportunity to respond but that their performance was not further impaired (compared to that of control rats) by the introduction of a delay. Conversely, rats with hippocampal lesions learned the response normally but had an impaired performance when a delay was introduced (Winocur, 1991). Thus, impairments in the delayed condition in these tasks suggest that the hippocampus is not functioning optimally.

Winocur and Gagnon (1998) also compared the performance of young and old Long–Evans rats in two tests, Olton's radial arm maze and a spatial non-matching-to-sample task in which older animals and animals with hippocampal lesions (Olton et al., 1986; Shaw and Aggleton, 1993; Winocur, 1982) are reliably impaired (Aggleton et al., 1989; Gagnon and Winocur, 1995; Geinisman et al., 1995). As expected, older animals demonstrated deficits in the performance of these tasks and a 100 mg/kg glucose injection improved their performance close to what was observed in young animals. Glucose improvement of performance was slight in the radial-arm maze and absent in the spatial non-matching to sample task. Following the glucose injection, blood glucose levels which were elevated in older animals were correlated with the level of performance of the animals in both tasks, in that worse glucoregulation was associated with poorer performance.

Other researchers showed that high blood glucose in 24-month-old male Lewis rats was associated with poorer reference memory performance (Blokland and Raaijmakers, 1993). Another experiment revealed that, in 24–26-month-old F344 rats, high blood insulin and to a lesser degree, high blood glucose following a 150 mg/kg glucose injection, was associated with poorer performance in a complex 14-arm maze (Long et al., 1992). However, the injection of 10, 100 or 500 mg/kg glucose did not improve performance in the maze when it was injected after three trials and retention tests the next day.

Stone et al. (1997) observed that the decrease in blood glucose regulation from 14 to 24 months in Sprague–Dawley rats was associated with a decreased performance in spontaneous alternation behavior during that period. Similarly, high blood glucose following a 500 mg/kg injection (suggesting poorer glucose regulation) was associated with impaired memory for an inhibitory avoidance training in 2-year-old Sprague–Dawley rats but not in 3-month-old rats (Stone et al., 1990).

Finally, in a series of experiments, we could not replicate the memory-improving action of glucose in a strain of mice (Balb/cJ) that otherwise demonstrated normal learning abilities (Messier, 1998) even though we observed the memory-improving effect of glucose in a related strain (Balb/cByJ) (Messier and Destrade, 1988). Many doses were examined, reducing the likelihood that the incorrect dose of glucose was used. The glucose-unresponsive strain had much lower blood glucose levels after a glucose injection, suggesting better glucoregulation. Another characteristic of this strain was a high resistance to the amnestic effects of scopolamine. One of the conclusions of these experiments was that glucoregulation somehow had an impact on cholinergic neurotransmission in the brain, whereas good glucoregulation was associated with no beneficial effect of glucose on memory and no impairing effects of scopolamine on memory. Conversely, poor glucoregulation was associated with memory improvement by glucose and susceptibility to the impairing effects of scopolamine.

Together, this series of experiments demonstrated that impaired glucoregulation in older animals and in animals fed high-fat diets is associated with impairment in tasks that depend on normal functioning of the hippocampus and that glucose specifically alleviates these deficits.

5.2. Human studies

A number of studies have also shown that poor glucose regulation is associated with impaired cognition. Two studies conducted in young university students compared the memory performance of students with better glucose regulation (those who had the smallest blood glucose rise following glucose ingestion) to the performance of students with poorer glucose regulation (Awad et al., 2002; Messier et al., 1999). It was found that students with poorer glucose regulation performed worse in tests of word free recall, paragraph recall or word order recall. In one of these experiment, glucose (50 g) improved the performance of students with poorer glucose regulation but not that of students with better glucose regulation (Messier et al., 1999). The effect of glucose was similar for easy to remember high-imagery words and for harder to remember low-imagery words. In the second experiment, glucose improved neither word recall nor paragraph recall but improved word order recall (Awad et al., 2002). Word order recall is a much more difficult task with the average performance being the correct recall of 30% of the words in a 20-word list. Donohoe and Benton (2000) performed a glucose tolerance test on undergraduate students and measured glucose every 30 min. They observed that between 2 and 3 h after the ingestion of 50 g glucose, there was a dip in blood glucose below fasting levels that was followed shortly by a return to fasting levels. They found that the quicker blood glucose returned to fasting levels, the better was the performance for paragraph recall. Other measures of glucose levels did not correlate with memory performance except that faster reaction time was associated with higher baseline blood glucose during the test performance. In general, the glucose tolerance in their participants was better (8.2 mmol/l) than the tolerance of our subjects with poor glucoregulation (peak glucose = 10.3 mmol/l).

As was discussed earlier, the effects of glucose on memory are much less in young participants than in older ones. Typically, older people tend to have worse glucoregulation. In a recent study, we compared the cognitive performance of older participants (age 55 to 84; mean age = 72 years) with better glucose regulation to the performance of older subjects with poorer glucose regulation as

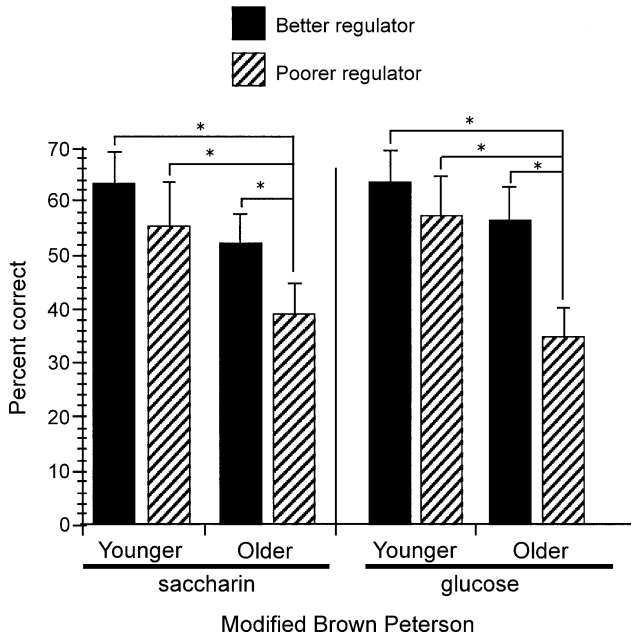

Fig. 4. Number of correct letters recalled in correct order (mean ± S.E.M.) on the modified Brown Peterson task during the counting condition for younger (55–72 years old) and older (>72 years) participants categorized as having better or poorer glucoregulation. The left panel presents the performance after drinking saccharin on one visit and the right panel presents the performance after drinking glucose on the other visit. By comparison, the average performance of university students on this task under the same conditions was 76.2 (reproduced from Messier et al., 2003).

measured by the increase of blood glucose from fasting to peak level following a glucose tolerance test (Messier et al., 2003). We also divided participants into older (72 years and over) and younger participants. In general, we found that older participants with poorer glucose regulation performed the worst in several tests, including an arithmetic task, verbal memory and the Brown Peterson task (Fig. 4). Glucose attenuated this deficit but only for the verbal tasks. Both the arithmetic and Brown Peterson tasks are thought to involve working memory and executive functions that depend more on frontal cortex functions. Similar relationships between indexes of glucose regulation and memory have been found in older adults (Craft et al., 1994; Hall et al., 1989). This pattern of results is similar to what was observed by Greenwood and Winocur (2001) in animals fed high-fat diets that lead to impaired glucose tolerance.

Kaplan et al. (2000) found similar results in older humans whereas people with high blood glucose tended to perform worse on paragraph recall and word list learning. In another study with older diabetic patients, higher glycosylated hemoglobin levels (a measure indicating poorer long-term glucose regulation) were associated with poorer performance in paragraph recall (Greenwood et al., 2003). Consistent with these findings, it was found in a recent experiment that older people with worse glucoregulation had a worse verbal memory performance (Convit et al., 2003). It was also found that reduced hippocampal volume was associated with poorer glucose regulation. Taken together, these results suggest that protracted hyperglycemia may be associated with brain dysfunction, particularly in the hippocampus.

These results are also consistent with the reported deficits, particularly in verbal memory, found in older people with type 2 diabetes (Biessels et al., 2002; Ryan and Geckle, 2000; Strachan et al., 1997). The extensive data on cognitive function in diabetes reviewed in the present issue support the general idea that impaired glucose regulation leads to cognitive impairments. At least three reports have shown that improvement of glucose regulation following drug treatment leads to cognitive improvements (Gradman et al., 1993; Meneilly et al., 1993; Naor et al., 1997).

Meneilly et al. (1993) evaluated the performance of older participants (mean age: 71 years) before and after 6 months of continued treatment with oral hypoglycemic agents. In a comparison of performance means of the baseline assessment and the 6-month assessment, the authors reported significant improvements for measures of mental agility, processing speed, modified cued recall and nonverbal reasoning. These results suggest that some cognitive improvement appear to be associated with improvement in glycemic control. Meneilly et al.'s (1993) study did not control for practice effects and a control group was not used to eliminate alternative interpretations of the results.

Gradman et al. (1993) compared 13 previously treated type 2 diabetes participants and 10 untreated type 2 diabetes participants to 13 controls (mean age: 67 years). Cognitive assessment was performed at baseline, 1 month after diabetic patients stopped taking their medication, and after 2 and 6 months of treatment with glipizide. It was reported that improvements in glycemic control were associated with improvement in a verbal memory task. After stopping their anti-diabetic medication for 1 month, previously treated type 2 diabetes participants had poorer performance in the memory task (Fig. 5). Two and six months after the reinstatement of anti-diabetic medication, diabetic patients recalled significantly more words than after 1 month of no medication, and the previously untreated type 2 diabetics also improved. After 6 months of treatment, previously untreated diabetics also improved significantly. The control group did not improve during that period, demonstrating

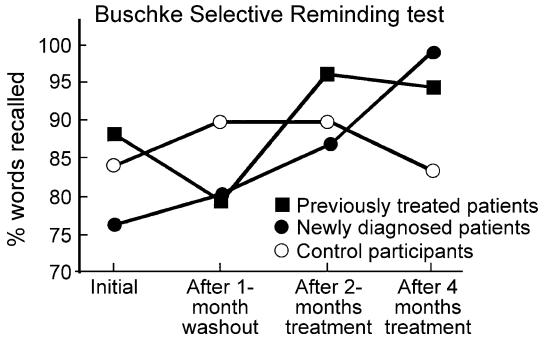

Fig. 5. Percentage of words recalled on the Buschke Reminding Test by diabetic patients before and after treatment with the anti-diabetic glipizide (adapted from Gradman et al., 1993).

that the effect observed in the diabetic group was not due to practice effects.

More recently, Naor et al. (1997) compared the performance of two groups of 20 type 2 diabetes patients who showed initial poor metabolic control (HbA_1 >10%; mean age for both groups: 64 years) before and after differential diabetes treatment (Naor et al., 1997). Patients assigned to the intensive treatment group underwent diabetes assessment and treatment to normalize glucose levels, and were provided with an individually adapted diet and daily monitoring of blood glucose to optimize their condition. The intensive treatment group improved for most cognitive measures, across the assessments. In the regular treatment group, performance either remained unchanged or even decreased across the assessments. The cognitive improvements observed in the intensive treatment group were correlated with improvement in glycemic control. This finding provides further support for the relationship between glycemic control and cognitive functions. These studies suggest that the degree to which glycemic control is achieved may also be an important factor mediating the impact of diabetes. This assertion is supported by other studies that have shown that high HbA1c levels are associated with poorer performance in verbal memory tasks (Greenwood et al., 2003; Reaven et al., 1990).

In conclusion, there is evidence that impaired glucose regulation is associated with impaired cognition, particularly episodic memory. This impairment is minimal in young people but increases in older people where it may compound other aging processes leading to reduced brain function. A few studies have shown that glucose improvement of memory is associated with poor glucose regulation, although this may not be the case for diabetic patients. Results of a few studies also suggest that drug treatments that improve glucose regulation also produce cognitive improvement in diabetic patients.

6. Conclusions

This review has addressed a number of issues related to the effect of glucose ingestion on cognitive processes. Originally, this effect was taken as the manifestation of a process by which reinforcers could facilitate memory. A number of experiments that did not replicate the effect of glucose on cognition suggest that this is not the case. One of the hypotheses put forward in this review is that glucose acts mainly to alleviate memory deficits associated with impaired glucose regulation. This hypothesis remains to be fully tested in experiments that specifically compare animals or humans with better or poorer glucose regulation. Glucose remains one of the few pharmacological tools that influences learning and memory processes in humans and can be used to manipulate cognitive processes. This review also examined a number of potential mechanisms that could underlie the impact of glucose on the brain. A number of results suggest the existence of peripheral mechanisms based on glucose-sensitive neurons. The mechanisms by which neurons are glucose-sensitive may depend on physiological events taking place when glucose is transported via glucose transporters. Some of the first metabolic steps that immediately follow the passage of glucose may also be implicated. A number of results also suggest that local glucose supply to the brain may limit neuronal activity in certain brain areas such as the hippocampus. This limitation may be due to increased demands on a metabolic pool associated with neurotransmitter synthesis. Alternatively, a decreased local supply of glucose may be due to changes in glucose transport that restrict glucose entry in the brain locally or alter the other metabolic routes taken by glucose to reach neuronal synaptic regions. The potential role of insulin in the observed effect of glucose on the brain remains largely unexplored due to the inherent difficulty of separating the action of insulin from that of glucose. Craft and Watson present in this issue many observations that suggest that insulin may play a role in pathological states including Alzheimer's disease. The wide distribution of insulin and insulin receptors in the brain as well as the presence of insulin-dependent glucose transporters suggest that brain insulin may participate in several undiscovered processes. The study of glucose effects on brain functions has resulted in the development of several new lines of investigation and the recent developments have provided crucial knowledge about the functional impact of local glucose metabolism, transport and utilization on neuronal functions.

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