Carbohydrate, Memory, and Mood
David Benton, Ph.D., and Samantha Nabb, B.Sc.

From a physiologic perspective, the role of glucose in brain functioning is reviewed and the effect of diet-induced changes in blood glucose on mood and cognition are outlined. Many studies have used a glucose drink or a meal composed almost entirely of carbohydrate as an experimental tool. Because pure sources of carbohydrate will be rarely consumed, the possibility that foods of different glycemic indices will modify mood and memory is briefly considered.

Key words: carbohydrate, glucose, glycemic index, memory, mood

Glucose and the Brain

Unlike other organs, the energy requirement of the brain is met almost exclusively by aerobic glucose degradation. The use of C\(^{14}\) labeled glucose shows that in the perfused brain, only 30% is oxidized directly to CO\(_2\) and water; much of the remainder is used for the synthesis of amino acids, peptides, lipids, and nucleic acids. Specifically, acetyl-CoA, a metabolite of glucose, is essential for the synthesis of the neurotransmitter acetylcholine, that plays a role in the modulation of memory.

The energy requirement of the brain is disproportionately large. When the body is at rest it accounts for approximately 20% of energy consumption, although it comprises only 2% of body weight. The energy stores in the brain are extremely small when compared with the high rate of glucose utilization, and the brain therefore relies on a continuous glucose supply. At the basal rate of consumption the glucose content of the brain would be exhausted in 10 to 15 minutes.\(^2\)

Traditionally, the concentration of glucose is thought to be the same throughout the brain. Consensus was that the ability to transport glucose exceeded the demand for fuel, ensuring that levels do not vary.\(^3\)\(^4\) This perspective views the uptake of glucose by the brain as largely independent of the level of blood glucose, although abnormally low blood glucose levels would limit transport across the blood-brain barrier. An equilibrium forms between the levels of glucose in the plasma and the brain’s extracellular fluid (ECF) such that higher levels of blood glucose are associated with higher levels of glucose in the brain.\(^5\)\(^6\)

Positron emission tomography (PET scan) involves an injection of glucose, usually with a radioactive label of F\(^{18}\). Because glucose goes to the most active areas of the brain PET establishes those areas important for a particular type of functioning. Such studies demonstrate that mental inactivity requires a lower rate of brain metabolism than when processing information. For example, light stimulation increases cerebral glucose metabolism in the occipital cortex, which processes visual information; similar changes can be measured in other areas of the brain after particular cognitive tasks.\(^7\)\(^8\) Thus, increased mental activity is associated with increased glucose metabolism. The use of PET scans illustrates that glucose in the blood enters the brain in a matter of minutes and is directed to those areas that are metabolically active. The major mechanism is thought to be capillary recruitment, that allows increased blood flow, and hence the provision of glucose to metabolically active areas.

Although the blood-brain barrier does not limit the supply of glucose, the model of the brain as being virtually always well supplied with glucose has come under question. The many reports that glucose administration improves the memory of both animals\(^9\)\(^10\) and humans\(^11\)\(^-\)\(^14\) particularly the elderly,\(^15\)\(^-\)\(^17\) need to be explained. That memory is enhanced when glucose is administered directly into the brain\(^18\) indicates that an increased central supply enhances functioning. The observation that increased provision of glucose enhances acetylcholine synthesis is additional evidence that the brain is sensitive to the provision of glucose.\(^19\)

The Supply and Demand for Glucose

The essential question that arises is whether the direction of blood flow to active areas of the brain is always sufficient to meet the demands for glucose. Partridge\(^20\) speculated that when the demand for glucose is very

Drs. Benton and Nabb are with the Department of Psychology, University of Wales Swansea, Singleton Park, Swansea SA2 8PP, Wales, United Kingdom.
high, there is a tendency for metabolically active regions of the brain to become locally neuroglycopenic, that is, they develop low intracellular levels of glucose. In freely moving rats, during a spatial working memory task, a decrease in hippocampal extracellular glucose has been reported. An injection of glucose, but not a placebo, prevented this decline in the level of glucose in the hippocampus and improved learning.21 Consistent with the decline in extracellular glucose reflecting an inability to locally maintain glucose concentrations, extracellular glucose levels in the hippocampus decreased by 32% when a complex maze was performed. By contrast, when a less complex maze was run, glucose levels fell by only 11%. The authors concluded that their data “strongly suggest that the observed decreases in hippocampal ECF glucose are associated with cognitive demand . . . it seems that memory processing by the hippocampus may be limited by the availability of glucose.”21

It is not possible to measure glucose concentrations in the human brain; nevertheless it has also been suggested that enhanced provision of glucose selectively benefits tasks that are cognitively demanding.13 Although it is difficult to quantify “cognitive demand,” the duration of the demand and its complexity can be considered. The provision of blood glucose has been found to influence the difficult rather than the easier trials of the Stroop test11 and to improve choice rather than simple reaction times.12 A glucose drink selectively influenced the more difficult tests of the Porteus Maze.13 In all of these instances it was the more demanding tasks that were susceptible to changes in blood glucose levels. When the duration of a task has been considered, blood glucose has been found to influence a vigilance task, but only towards the end of the test session.22,23 In a driving simulator glucose only influenced performance after driving 70 kilometres.23 Thus it is only the later stages of prolonged tasks that are susceptible to the provision of glucose. A final line of evidence that the provision of glucose may on occasion limit neural functioning comes from a study that made the assumption that when performing verbal tasks, the more metabolically active left hemisphere would be partially depleted of glucose. The prediction was confirmed that increased levels of blood glucose would specifically benefit memory for information directed to the left rather than right hemisphere.24

Glucose and Memory

The mechanism by which an increased supply of glucose enhances memory is poorly understood. One possibility is that the synthesis of the neurotransmitter acetylcholine is increased. The role played by acetylcholine in the modulation of memory has been frequently considered.25,26 The evidence is of various types. Firstly, there are consistent reports that Alzheimer’s disease, which is characterised by a profound failure of memory, is associated with a depletion of cholinergic neurons. Secondly, drugs that block the action of acetylcholine disrupt the memory of both animals and humans. Thirdly, therapeutic drugs prescribed to improve the memory of Alzheimer’s patients often act by increasing cholinergic activity.

The enzyme choline acetyl transferase, found in the presynaptic nerve terminal, converts the precursors choline and acetyl CoA to acetylcholine. Glucose is the main source of the acetyl groups of acetyl CoA.27 Glycolysis converts glucose by a series of steps to pyruvate, that in turn is broken down by the pyruvate oxidase system to form acetyl CoA. Choline acetyltransferase is not a saturated enzyme, thus an increased supply of acetyl CoA, resulting from increased glucose metabolism, is associated with increased production of acetylcholine.

In rats that have not eaten for 24 hours brain acetylcholine levels are lower, something that can be restored by feeding normal food or by administering glucose and choline.26 A review concluded that under resting conditions increased glucose availability has little effect on acetylcholine levels in continuously fed animals.19 When there is a high demand for acetylcholine, however, a high availability of glucose increases the rate of the synthesis of the transmitter by increasing the production of acetyl CoA. Using the uptake of choline as an index of cholinergic activity, investigators found that a glucose injection increased acetylcholine synthesis in mice.19 Raising glucose levels reportedly increases the release of acetylcholine from the rat hippocampus, an area of the brain important in modulating memory.20 In mice, increasing glucose levels attenuated the amnesia induced by the anticholinergic drug scopolamine.19,30 Taken together these animal studies provide strong evidence that, under periods of neuronal activity, raising the glucose supply is associated with an increased synthesis of acetylcholine, which benefits memory.

Glucose influences many neurotransmitter systems and can modify the impact on memory of drugs that act via opiate, GABAergic, glutaminergic, and cholinergic sites.10 Peripheral injections of glucose have been shown to suppress the firing of nigrostriatal dopamine-containing neurons31 and to lower the level of dopaminergic metabolites.32 When drugs are injected directly into the brain, the action of glucose is more specific and the nature of its action varies with brain site. For example, the amygdala is an area of the brain that influences memory for emotional events. The opiate agonist morphine, when injected into the amygdala, impairs the avoidance learning of rats, an effect that is attenuated by the injection of glucose into the same brain area.33 The septohippocampal system is important for the learning of spatial tasks. The injection of glucose into the medial

S62 Nutrition Reviews®, Vol. 61, No. 5

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.
septum antagonized the behavioral influence of morphine but not the cholinergic drug scopolamine or the adrenergic drug propranolol. These studies illustrated that glucose acts in a selective manner, in particular, influencing opiate mechanisms. Data suggest that opiate mechanisms influence cholinergic functioning. Opiate receptors in the septum inhibit the release of acetylcholine from the hippocampus; morphine injected into the medial septum reduced the release of acetylcholine in the hippocampus, an effect blocked by the co-injection of glucose.

The Type of Carbohydrate, Meals, and Memory

Various strands of evidence question the assumption that the ability to transport glucose to particular areas of the brain never influences neural functioning. If the provision of glucose to the brain on occasion limits cognitive performance, the question arises as to whether diet plays a role. Do the patterns of meals and the glycemic load of the diet modulate functioning? Although there have been no studies of the association between glycemic load and memory, there are good reasons to suggest that there may be an association. Given the suggested relationship between glycemic load and type 2 diabetes, and the association between poor glucose tolerance and cognitive decline, the possibility that glycemic load will influence cognitive functioning should be explored.

Meals may also have a shorter-term influence. On a number of occasions, memory and school performance have been influenced adversely by missing breakfast. In an Israeli study, however, the effect was short term, explained by the authors as a reflection of the short-term increase in blood glucose that follows a meal. There is evidence of a possible role for glucose in the memory-enhancing effect of breakfast. In adults memory performance two hours after breakfast was found to correlate with blood glucose values, and the adverse effect of missing breakfast was reversed by giving a glucose-containing drink.

A recent study provided breakfasts containing an equal amount of carbohydrate; in one diet the carbohydrate source was mostly in the form of slowly (SAG) rather than rapidly available glucose (RAG). The SAG breakfast benefited memory later in the morning; RAG had no effect.

In a sample of elderly people, three types of carbohydrate were consumed: glucose, instant potato, or barley. Although memory was better after the consumption of both potato and barley, improvement was not associated with the level of plasma glucose. The consumption of the low-glycemic index barley improved memory more than potato.

In summary, although increased glucose supply enhances memory in humans and animals, it is an effect that appears to be stronger in the elderly and depends on the nature of the test. There have been few attempts to consider the effect of the glycemic index of carbohydrates on memory, although paradoxically the limited data available suggest that a food with a low glycemic index may be beneficial. Given the known effect of low-glycemic index foods to improve glucose tolerance, the possible role of this mechanism should be considered.

Carbohydrate Intake, Serotonin, and Mood

A related suggestion is that the level of blood glucose influences mood. Many people consume sugary snacks when they are feeling low or in need of energy. The opposite suggestion has also been proposed, that the intake of carbohydrate is calming because it increases the synthesis of serotonin in the brain. Some have suggested that individuals eat high-carbohydrate foods for a psychopharmacologic effect, to improve mood, for example, those suffering with Seasonal Affective Disorder (SAD) and premenstrual syndrome (PMS).

The increase in blood glucose following the consumption of carbohydrate is associated with the release of insulin. Insulin causes the large neutral amino acids (LNAA: tyrosine, phenylalanine, leucine, isoleucine, valine) to be taken up into muscle although tryptophan is bound to albumin in the blood. A meal comprising almost totally carbohydrate thus increases the ratio of tryptophan to LNAA in plasma. The LNAA and tryptophan compete for a transporter molecule. When a high-carbohydrate meal increases the tryptophan-to-LNAA ratio, therefore, relatively more tryptophan is transported into the brain where it is metabolized into the neurotransmitter serotonin. Although in animals the intake of pure carbohydrate is associated with increased serotonin synthesis, in humans, even when the level of tryptophan increases, there is no evidence of an increased release of serotonin. When 30 human studies were summarized, meals that were almost totally carbohydrate were found to have increased the tryptophan-to-LNAA ratio in the blood. However, although when protein comprises less than 2% of total calories, there was more tryptophan available, as little as 5% of the calories in the form of protein was enough to ensure that this phenomenon did not occur. The improbability of eating meals that contain such a low level of protein raises considerable doubt as to importance of this mechanism as a part of normal diet. In foods that many would classify as high in carbohydrate, such as bread, rice, or chocolate, there are levels of protein sufficient to prevent an increase in the availability of tryptophan.

In many women at the end of the monthly cycle there is an increase in appetite and food consumption. It has been concluded that "individuals with PMS increase
their carbohydrate consumption in the pre-menstrual stage." A study providing an experimental meal that contained no protein decreased the depression, anger, and confusion of those with PMS. Reviews of the topic find a significant increase in energy intake during the luteal phase, and there is evidence of increased basal metabolic rate. However, one must distinguish increased carbohydrate intake from increased intake of all macronutrients. The question arises as to whether the anecdotal observation of increased craving for sugary items results in characteristic changes in macronutrient intake. An isolated study found that there was an increased intake of carbohydrate but not other macronutrients; however, the vast majority of studies do not share these observations. The weight of evidence is that carbohydrate intake is not selectively increased in the premenstrual stage. Although there is support for anecdotal statements that cravings for sweet, pleasant-tasting foods increase, the driving force is likely to be an increased consumption of food items containing carbohydrate and fat rather than an increased appetite for carbohydrate.

Similarly, investigators have suggested that those suffering with SAD have a specific hunger for carbohydrate, a mechanism suggested to improve mood. A review of the topic, however, concluded that there was little evidence to support a specific hunger for carbohydrate although there may be a preference for pleasant-tasting foods.

Long-term Carbohydrate Intake and Mood

Although the modulation of serotonin levels is not a credible mechanism, there are several studies that have reported that the cumulative intake of carbohydrate was associated with better mood. Based on food diaries kept over nine days, a negative relationship was found between the proportion of energy consumed as carbohydrate and depression. The association was not between meals and mood around the time of eating, but over several days there was a cumulative impact. More recently, 686 individuals were asked at midday to report their mood and what they had eaten that morning (Benton, unpublished finding). The more carbohydrate that people had consumed, the happier male subjects reported they had been during the morning. In both of these studies the intake of protein was sufficient to prevent an increase in the plasma tryptophan-to-LNAA ratio. When experimental diets containing low, medium, or high levels of carbohydrate were consumed for a week, the low-carbohydrate diet was associated with increased anger, depression, and tension. This report supported the finding that eating a low-carbohydrate, high-protein breakfast for three weeks resulted in increased levels of anger. When a group of young German women dieted for six weeks, those whose meals were based on cereals and vegetables, rather than meat and fish, reported better mood. Eating experimental diets that are higher in carbohydrate are therefore associated with better mood. The repeated finding that carbohydrate intake has a cumulative influence suggests the need to examine the impact of glycemic load on mood.

The Short-term Effect of Carbohydrate on Mood

Studies of the short-term impact of carbohydrate on mood have either compared sugar- or starch-based foods with those offering high levels of protein; alternatively, they have provided a sucrose- or glucose-containing drink. When a protein-rich meal such as turkey breast was compared with a carbohydrate-rich meal, the latter tended to result in subjects feeling less energetic. Studies comparing the consumption of a sugar-containing drink and a calorie-free drink have produced equivocal findings; two found increased subjective energy and three others reported nonsignificant findings.

A major variable appears to be the time after consumption when mood was assessed. The studies reporting decreased subjective energy after a carbohydrate-containing meal measured mood approximately two hours after consuming the drink or meal. By contrast, when subjective energy was found to increase after a sugar-containing drink, this occurred after 15, 30, or 60 minutes. Benton and Owens, who used by far the largest sample sizes in this area, commented that the short-term increase in reported energy seemed to be a robust phenomenon as they replicated the finding. It was, however, a small effect that would likely not be reproduced in a small sample size. The report that people consuming a sugary snack experienced a short-term increase in energy followed by a longer-term fall in subjective energy is consistent with a two-stage effect. Although many of these studies used a source of pure glucose and hence had the potential to increase the tryptophan-to-LNAA ratio, at least some of the effects on mood were too rapid for increased serotonin synthesis to have occurred.

Mood Under Demanding Conditions

The possibility that increasing blood glucose maintains mood when sustained demands are placed on an individual has been little considered. When mood was assessed before and after performing three cognitively demanding tasks, falling levels of blood glucose were associated with lower self-reported energy. That the tasks in this series placed greater cognitive demands on subjects than in previous studies may be an important factor in the association between falling blood glucose and falling
levels of subjective energy. One can speculate that the association between falling blood glucose and falling subjective energy may be the consequence of localized neuroglycopenia, a result of the demanding cognitive tasks that had been performed. Previously investigators reported that subjects whose blood glucose remained low reported greater tension than those whose blood glucose levels were higher.\textsuperscript{71}

**Individual Differences in the Control of Blood Glucose**

Finally, when considering the association between diet, blood glucose levels, and psychological functioning, it is essential to take into account individual differences in physiology. In Peruvian Indians known for their aggressiveness,\textsuperscript{78} violent offenders,\textsuperscript{79,80} and undergraduates who report themselves as irritable,\textsuperscript{81,82} a greater degree of aggressiveness has been associated with a tendency for rapidly falling blood glucose levels during a glucose tolerance test. The possibility of a causal relationship between blood glucose levels and aggressiveness was supported by reports in both children\textsuperscript{83} and adults,\textsuperscript{71} in which raising blood glucose levels with a sugar-containing drink led to less irritable behavior.

One must also take into consideration individual differences in the ability to regulate blood glucose when considering cognitive functioning. Better glucose tolerance was associated with better cognition in rats,\textsuperscript{84} young humans,\textsuperscript{12} the healthy elderly,\textsuperscript{15,17} and those suffering with Alzheimer’s disease.\textsuperscript{16} Better glucose tolerance is displayed when blood glucose levels fall rapidly, following a rise after a glucose drink. Because meals with a low glycemic load improve glucose tolerance,\textsuperscript{85} the above data suggest a differential impact of foods with a different glycemic index on mood and cognition, although the question has not yet been addressed systematically.

**Conclusion**

There is growing evidence that the provision of glucose may influence both memory and mood, particularly when intense metabolic demands are placed on the brain. Individual differences are important: those with better glucose tolerance have better mood and memory. In the future, investigators should consider the possibility that the nature and schedule of meals and snacks can influence psychological functioning. Diets of different glycemic load have the potential to influence the pattern of glycoemic supply and to modify glycoemic tolerance; both of these have the potential to influence the way the brain functions.

22. Benton D. The impact of increasing blood glucose


56. Buffenstein R, Poppitt SD, McDevitt RM, Prentice


