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ORIGINAL INVESTIGATION

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The influence on cognition of the interactions between lecithin, carnitine and carbohydrate

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Abstract It is accepted that acetylcholine-mediated neurones modulate memory. As lecithin, carnitine and glucose all influence acetylcholine metabolism, the possibility of synergistic interactions was considered. Four hundred young adult females randomly, and under a double-blind procedure, received capsules for 3 days that contained a placebo, lecithin (1.6 g/day), carnitine (500 mg/day) or carnitine plus lecithin. A battery of cognitive tests was administered prior to taking the capsules, after 3 days of taking the supplements, and for a third time after consuming either a glucose drink or a placebo. Reaction times were more rapid when carnitine and a glucose drink were taken together. Memory was enhanced in those taking a glucose rather than placebo drink. Neither mood nor the ability to sustain attention were influenced by these procedures. The hypothesis that memory would be facilitated by offering supplements of lecithin, carnitine and glucose was not supported.

Keywords Carnitine · Glucose · Lecithin · Memory · Reaction times

Introduction

For many years it has been accepted that acetylcholine-mediated neurones are involved in human memory (Freo et al. 2002; Messer 2002). For this reason the impact of drugs and food-related items, which are thought to enhance acetylcholine activity, have attracted attention. The present study examined the possible synergistic interaction among three substances—lecithin, carnitine and glucose—as it has been suggested that each enhances the synthesis and release of acetylcholine. Acetylcholine is synthesised from acetyl-CoA and choline by the enzyme choline acetyltransferase. Under normal conditions, the supply of acetyl-CoA depends on the breakdown of glucose via the glycolytic pathway. Although choline can be synthesised in the body, much of the bodily level is thought to result from dietary intake of lecithin, that is choline covalently bound to a phospholipid. Carnitine plays a role in the transport of acetyl-CoA. If a deficit of acetylcholine causes problems of memory, it is obvious to suggest that enhancing the capacity to synthesise acetylcholine levels in the brain may benefit memory.

An enhancement of memory following a glucose drink has been found in both elderly (Gonder-Frederick et al. 1987; Hall et al. 1989; Manning et al. 1990; Craft et al. 1992, 1993) and younger adults (Lapp 1981; Hall et al.1989; Benton and Owens 1993; Benton et al. 1994). In both adults (Moser et al.1983; Benton 1990; Benton et al. 1994) and children (Benton et al.1987), a glucose drink has been found to improve the ability to sustain concentration. Keul et al. (1982) found that the number of errors made in a driving simulator decreased when a glucose drink was taken.

Among various possible mechanisms that could mediate the impact of glucose on memory, the facilitation of cholinergic mechanisms has attracted particular attention. Glucose is the principal source of acetyl groups for the acetyl-CoA necessary for the synthesis of acetylcholine. In rats, a 24-h fast is associated with lowered levels of brain acetylcholine levels, something that can be restored by either feeding or administering glucose and choline (Kuntscherova 1972). Messier et al. (1990) reviewed the topic and concluded that when rested animals were fed continuously, increased glucose availability had little effect on acetylcholine levels. However, when there is a high demand for acetylcholine, a high availability of glucose increased the rate of synthesis of the transmitter by increasing the production of acetyl-CoA. Messier et al. (1990) used the uptake of choline as an index of cholinergic activity and found that in mice a glucose injection increased acetylcholine synthesis. Durkin et al. (1992) produced the first direct experimental evidence that raised

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glucose levels facilitate acetylcholine synthesis, by measuring its release from the rat hippocampus under conditions of increased neuronal activity. Taken together, these animal studies provide powerful evidence that, under periods of neuronal activity, a raised glucose supply is associated with an increased synthesis of acetylcholine.

No recommended daily intake for carnitine has been set in either the USA or the UK, as it suggested that well-nourished adults can synthesise adequate amounts. However, it is possible that sub-clinical deficiencies of carnitine exist and alternatively carnitine may prove to have pharmacological properties. Animal products are the best dietary sources of carnitine. Carnitine is, however, synthesised in the liver and kidney from the essential amino acids lysine and methionine (Borum 1983). There is little doubt of the importance of carnitine in bodily functioning. Amongst several other actions, it buffers the ratio of bound coenzyme A to free coenzyme (Pettegrew et al. 2000) and may play an important role in ensuring that an adequate supply of acetyl-CoA is available to allow acetylcholine synthesis to proceed.

Acetyl-L-carnitine (ALC) is the acetylic derivative of L-carnitine. As the enzymes that are involved in the synthesis of ALC are present in several areas of the brain (Marquis and Fritz 1965), it is assumed that ALC plays a role in the regulation of neuronal transmission (Shug et al. 1982). ALC also has a slight cholinergic activity (Blum et al.1971; Falchetto et al. 1971), particularly when an acetylcholine-induced stimulation is also present. These cholinergic effects have been observed electroencephalographically in the visual cortical area (Onofrj et al. 1963, 1987; Tempesta et al. 1982) and in vitro where ALC has been found to increase acetylcholine formation (Thomitzek 1963). ALC has also been reported to increase the binding of glucocorticoids (Angelucci et al. 1986a) and nerve growth factor (Perez et al. 1988) in the hippocampus, an area of the brain known to play an important role in memory. A meta-analysis of the studies of ALC concluded that it helped significantly those with "mild cognitive impairment or preventing deterioration" (Montgomery et al. 2003).

Higgins and Flicker (2000) performed a meta-analysis of 12 studies that had considered the impact of lecithin on Alzheimer's patients and found that no trial reported lecithin to produce a clear benefit. They concluded that "evidence from randomised trials does not support the use of lecithin in the treatment of patients with dementia." They did not, however, feel able to rule out totally a small or moderate effect, although the results of the small trials to date did not make a large trial a priority.

It was perhaps optimistic to expect that such a serious disorder as Alzheimers disease, which results in a dramatic loss of the brain's weight, would respond to a change in diet. You could argue that it is more likely that younger and healthier subjects will respond, as they have a more intact set of acetylcholine-mediated neurones. In studies of lecithin in healthy subjects, two studies (Ladd et al. 1993; Safford and Baumel 1994) have reported significant effects on memory and two have not (Drachman et al. 1982; Harris et al. 1983). It may be important that those studies that report positive findings used a larger number of subjects (80 & 61 subjects) than those studies with negative findings (16 & 9 subjects).

As lecithin, choline and glucose have each been reported to both facilitate memory and enhance acetylcholine functioning, the question posed by the present study was whether they have a synergistic action and, thus, facilitate cognitive functioning.

Methods

Subjects took the battery of cognitive tests and then randomly and, under a double-blind procedure, were allocated to groups taking one of the four capsules. Following baseline testing, four capsules were taken each day for 3 days, after which the cognitive battery was taken for a second time. Randomly and blindly subjects then consumed either a placebo or glucose drink, and after 30 min took the cognitive tests for a third time.

Subjects

Four hundred females undergraduates, mean age 21.8 years, were recruited when they responded to a poster. They gave written informed consent and were paid £20 (pounds sterling) for taking part. The procedure was approved by the local ethics committee. No subject was taking similar supplements and all were in good health. All subjects completed the trial.

Supplements

Each day subjects took one of the following: (a) placebo (neutral lipid preparation), (b) lecithin containing 70% phosphatidylcholine (four capsules a day offered 1.6 g phosphatidycholine), (c) carnitine (as tartrate) 500 mg, (d) lecithin 1.6 g plus carnitine 500 mg. Four capsules were taken each day, two in the morning and two in the evening.

Cognitive tests

Recall of word list

Three lists of 30 nouns, all of five letters and one syllable in length, were created. Nouns were selected on the basis of high frequency, high imagery and high concreteness (Paivio et al.1968). They were presented at the rate of one word per second. Immediately after presentation, subjects wrote down as many words as they could recall in 2 min. Approximately 20 min later, following the other tests, the subjects again tried to recall the words.

Reaction times

The reaction time procedure was based on that of Jensen (1987). On a panel, eight lamps were arranged in a semicircle 5.5 inches from a central button (the home key). The index finger was placed on the home key. Following a warning tone, one of the eight lamps illuminated and the subject pressed the button in front of that lamp. The decision time (DT) is the time taken to lift the finger from the home key. Simple and choice decision times when two, four or eight lamps could be potentially illuminated were measured over 20 trials.

Rapid information processing task

A computer generated a series of digits at the rate of 100 digits per minute for 5 minutes. Subjects pressed the space bar when they detected target sequences of three consecutive odd, or three

consecutive even, digits. Eight of these sequences were presented every minute. The number of correct and incorrect responses was analysed.

Mood assessment

The bipolar profile of mood states questionnaire (POMS; McNair et al. 1981) was used to rate how the subjects felt "during the past week". The POMS produces six scores that correspond to the basic dimensions of mood: energetic, clear headed, composed, confident, elated and agreeable. An overall mood score was created by adding the six dimensions as suggested by the manual.

Side effects

After taking the capsules, the subjects were asked if they had experienced side effects and whether they believed they were taking the active capsules, placebo or were unable to guess.

Statistical analysis

Mood was examined using a two-way analysis of variance; active capsule/placebo × time (before/after taking the capsule), with the latter as a repeated-measures factor. The effect of the drink was explored with a two-way analysis of variance; active capsule/placebo × drink (glucose/placebo). Vigilance was considered initially using a three-way analysis of variance, with repeated measures over two factors; active capsule/placebo × time (before/after taking the capsule) × minute of the test. Second, the impact of drink was examined with an active capsule/placebo × drink × minute design, with the last as a repeated-measures factor. Decision times were analysed with an active capsule/placebo × number of lamps monitored × time design. After the drink, the design used was active capsule/placebo × drink × number of lamps monitored. Finally, memory was considered with an active capsule/placebo × time × immediate/delayed recall analysis of variance, with the last two factors as repeated measures. Drink was examined with an active capsule/placebo × drink × immediate/delayed recall design.

Results

Mood

When the influence of the three active capsules was compared with the placebo, the interaction and type of capsule consumed × before/after taking the capsule did not reach statistical significance with any of the six mood dimensions. Similarly, when placebo or glucose containing drinks were compared, in no instance did either the main effect of drink or a drink × capsule interaction reach significance. In summary, mood was not influenced by these supplements or drinks.

Reaction times

Table 1 reports the median decision times with 1, 2, 4 and 8 lamps both before and after taking the capsules. Two interactions are listed; the active capsules/placebo × before/after taking the capsules (time); the active capsule/placebo × before or after taking the capsules × number of lamps monitored. Table 1 reports that none of the capsules influenced the decision times in the choice reaction task.

Table 2 lists the decision times, for each of the four numbers of lamps, following the taking of either a placebo or glucose drink. Only in the case of carnitine was there a significant effect. Figure 1 shows that irrespective of the number of lamps monitored, the decision times were faster ($F_{1,98}$=4.61, P<0.03) following the glucose than the placebo drink.

Vigilance

As various subjects choose the strategy of responding frequently, and not worrying if they made errors, those who made more than ten errors in any minute were excluded; this left just over 90% of the population. Table 3 lists the effects of the various treatments on the number of errors made in 5 min on the vigilance task. Neither the various capsules alone, nor the taking of a glucose or placebo drink, influenced performance. The only higher order interaction to reach significance was the capsule × time × minute of the test when lecithin was examined ($F_{4,692}$=3.07, P<0.02). Essentially the number

Table 1 The influence of supplementation on decision times of the choice reaction time task. The data are the mean ±SD of the median decision times, in milliseconds, for the 20 trials with each of the four lamps. The two interactions from the analysis of variance are reported where the test capsules are contrasted with the placebo

	1 Lamp	2 Lamps	4 Lamps	8 Lamps	Comparison with placebo
Before placebo	320	326	354	417	
	±59	±42	±45	±83	
After placebo	310	333	359	416	
	±48	±44	±46	±69	
Before lecithin	317	323	350	420	Capsule × time
	±51	±40	±40	±73	$F_{1,198}$=1.37, n.s.
After lecithin	300	325	349	412	Lamp × capsule × time
	±36	±37	±46	±70	$F_{3,594}$=0.09, n.s.
Before carnitine	323	323	348	410	Capsule × time
	±69	±38	±38	±75	$F_{1,198}$=0.07,n.s.
After carnitine	304	331	359	411	Lamp × capsule × time
	±38	±35	±40	±62	$F_{3,594}$=0.73, n.s.
Before lecithin + carnitine	319	320	351	418	Capsule × time
	±65	±40	±39	±86	$F_{1,198}$=1.37, n.s.
After lecithin + carnitine	302	329	355	403	Lamp × capsule × time
	±39	±38	±40	±64	$F_{3,594}$=1.19, n.s.

Table 2 The influence of a glucose or placebo drink on decision times in a choice reaction task. The data are mean ±SD for median decision times measured in milliseconds. In all instances, the degrees of freedom were 1 and 196

	1 Lamp	2 Lamps	4 Lamps	8 Lamps	*F* values
Placebo + placebo	310 ±48	328 ±47	354 ±48	401 ±59	
Placebo + glucose	300 ±37	323 ±37	348 ±43	400 ±79	
Lecithin + placebo	304 ±44	325 ±40	347 ±37	398 ±67	Drink F=0.01, n.s.
Lecithin + glucose	307 ±43	325 ±45	347 ±44	410 ±82	Capsule × drink F=0.52, n.s
Carnitine + placebo	310 ±42	340 ±44	358 ±43	416 ±58	Drink F=3.2, P<0.07
Carnitine + glucose	296 ±36	322 ±38	347 ±38	395 ±51	Capsule × drink F=0.87, n.s.
Lecithin/carnitine + placebo	303 ±35	332 ±47	353 ±38	408 ±67	Drink F=0.90, n.s.
Lecithin/carnitine + glucose	303 ±49	326 ±40	346 ±40	393 ±62	Capsule × drink F=0.02, n.s.

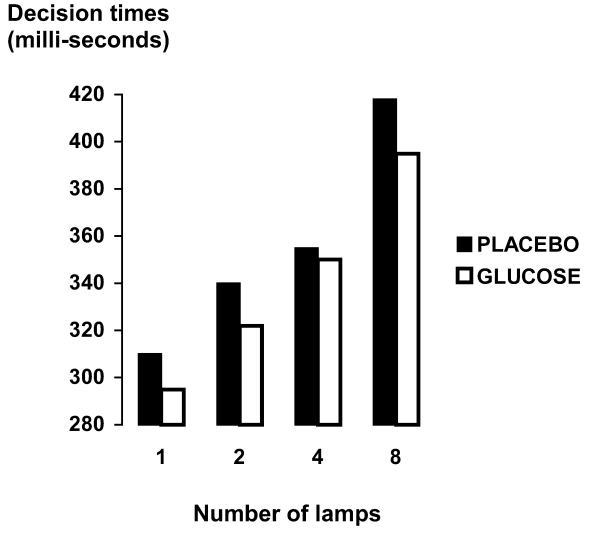

Fig. 1 The effect of a glucose or placebo drink on the decision times of those taking carnitine. The data are mean decision times in those who had taken the carnitine and either a glucose or placebo drink

correct was greater for the placebo group the longer the test was performed.

The number of sequences identified correctly is reported in Table 4. Although the taking of a drink did not influence performance, with all three active capsules there were significant two-way interactions. Performance was poorer following the taking of the active capsules rather than the placebo. The only higher order interaction to reach significance was the capsule × time × minute of the test in the case of lecithin ($F_{4,692}$=3.07, P<0.02). After taking the supplements the placebo group correctly reported more target sequences particularly towards the end of the test. As the interaction capsules × time summarises these data, with little loss of information, it is reported for brevity.

Memory

The impact of supplementation on recall of the word list is summarised in Table 5; no capsules influenced recall of the word list. When considered overall, the interaction capsule × time ($F_{3,392}$=2.19, P<0.08) approached statistical significance. In those who had taken lecithin, the

Table 3 The influence of supplementation on the number of errors made in the vigilance test. The data are mean number of errors over the 5-min period ±SD. *D*×*C* drink × capsule

	Before capsules	After capsules	Comparison with placebo	Placebo drink	Glucose drink	Comparison with placebo
Placebo	15.1±6.0	7.6±9.5		7.1±6.7	5.3±5.7	
Lecithin	14.5±13.9	10.1±14.2	Capsule × time $F_{1,180}$=2.02, n.s.	5.6±6.5	6.4±6.8	Drink $F_{1,178}$=0.23, n.s. Drink × capsule $F_{1,178}$=1.54, n.s.
Carnitine	15.2±12.5	10.5±17.4	Capsule × time $F_{1,180}$=1.16, n.s.	6.8±6.9	6.6±7.2	Drink $F_{1,178}$=0.89, n.s. Drink × capsule $F_{1,178}$=0.51, n.s.
Lecithin + carnitine	12.8±11.0	7.4±7.5	Capsule × time $F_{1,180}$=1,24, n.s.	7.1±7.1	5.5±5.2	Drink $F_{1,178}$=3.22, n.s Drink × capsule $F_{1,178}$=0.00, n.s.

Table 4 The influence of supplementation on the number of targets identified correctly in the vigilance test. The data are the mean number of sequences correctly identified in 5 min ±SD

	Before capsules	After capsules	Comparison with placebo	Placebo drink	Glucose drink	Comparison with placebo
Placebo	20.6±6.5	23.5±6.8		23.8±6.7	25.0±7.2	
Lecithin	20.2±5.8	21.4±6.7	Capsule × time $F_{1,173}$=4.87, P<0.03	23.1±7.0	23.2±6.2	Drink $F_{1,171}$=0.64, n.s. Drink × capsule $F_{1,171}$=0.44, n.s.
Carnitine	21.2±6.4	22.3±6.6	Capsule × time $F_{1,170}$=5.14, P<0.02	24.0±7.9	22.6±6.5	Drink $F_{1,168}$=0.04, n.s. Drink × capsule $F_{1,168}$=0.74, n.s.
Lecithin + carnitine	20.6±6.2	22.1±6.6	Capsule × time $F_{1,175}$=3,90, P<0.05	23.7±7.9	21.9±6.9	Drink $F_{1,173}$=0.02, n.s Drink × capsule $F_{1,173}$=2.31, n.s.

Table 5 The influence on supplementation on memory of a word list. The data are mean words recalled ±SD

		Before capsules	After capsules	Comparison with placebo
Placebo	Immediate	12.6±3.3	11.6±4.0	
	Delayed	10.7±3.4	8.9±4.0	
Lecithin	Immediate	13.3±3.6	11.0±3.3	Capsule × time
	Delayed	10.8±3.8	8.4±3.8	$F_{1,198}$=0.98, n.s.
Carnitine	Immediate	12.7±3.4	10.6±3.7	Capsule × time
	Delayed	10.4±3.7	8.0±3.7	$F_{1,198}$=0.34, n.s.
Lecithin + carnitine	Immediate	12.8±3.6	11.1±3.8	Capsule × time
	Delayed	10.4±3.9	8.1±3.7	$F_{1,198}$=0.72, n.s.

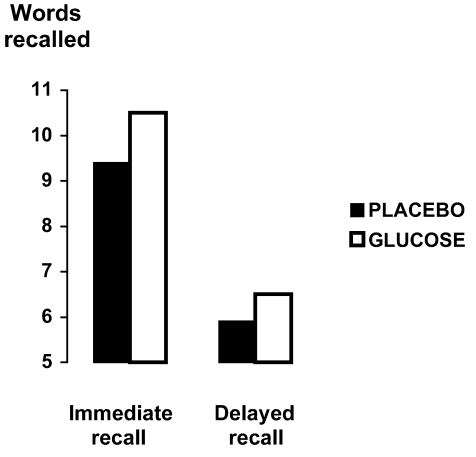

Fig. 2 The influence of glucose and placebo drinks on memory. The data are mean words recalled in those who had taken the placebo or carnitine

glucose drink was associated with poorer performance, whereas with the other three types of capsule the glucose drink was associated with better recall of the word list. If the lecithin group was removed from the analysis, then the type of drink reached statistical significance ($F_{2,294}$=4.79, P<0.03), those taking glucose recalled more than those taking the placebo. Figure 2 illustrates that taking a glucose rather than placebo drink, in these three groups, was associated with better memory. The capsule × drink interaction was again non-significant ($F_{2,294}$=0.15, n.s.).

Of the subjects, 92% reported no side effects. The minority who reported some reaction were found in almost similar numbers amongst those taking each of the four types of capsules. The side effects, when noted, were of a minor nature. For example subjects reported feeling either more or less tired or hungry, having a headache or stomach ache. There was no reason to suggest that there was a widespread or systematic adverse or positive response to any of these capsules. When asked, at the end, to guess whether an active supplement or a placebo had been consumed, of those in fact taking the placebo 10% guessed they had the placebo, 15% an active supplement and 75% did not know. Of those taking the active supplements, 17% guessed they had consumed a placebo, 13% an active supplement and 70% could not say. The evidence was that the double-blind procedure was successful.

Discussion

Although the introduction outlines some of the evidence that lecithin, carnitine and glucose all influence acetylcholine synthesis and memory, the present results produced only limited evidence of synergistic interactions. In drawing this conclusion, it is important to remember the parameters examined in the present study, and to be cautious when generalising to other situations. The dose used, the duration of administration, the sample used and the tests administered are all potentially important variables.

Unlike the majority of previous studies, lecithin was administered for only 3 days rather than weeks or months. The dose, 1.6 g phosphatidylcholine, contrasts with doses in excess of 20 g (of less-pure lecithin) given in some previous studies. The dose in the present study was chosen to represent a dietary supplement rather than a pharmacological dose. It is possible that a chronic rather than a short-term supply of lecithin might have a beneficial influence.

Is the duration of the administration of lecithin important? Ladd et al. (1993), in one of the few studies that used a single dose, administered 25 g lecithin (55% phosphatidylcholine giving 2.06 g choline) and found that it improved memory after 90 min. They did not, however, find a similar reaction with 10 g of their lecithin preparation. Wurtman et al. (1976) reported that a dose of 33 g lecithin, offering 0.76 g choline, raised serum choline levels for 4–8 h to about 200% of baseline (Wurtman et al. 1976). So there is evidence that an acute dose of lecithin offers an enhanced supply of choline in the blood. It is, however, important to distinguish potential short-term from longer term benefits.

The objective of the present study was to consider the possible benefits of a short-term increased supply of choline with the implicit suggestion that acetylcholine would be synthesised at an increased rate. The possibility that an increased supply of lecithin over a longer period might have other benefits, for example altering phospholipid metabolism, cannot be excluded. In other circumstances, it has proved necessary to administer lecithin for a longer period; for example, Bartus et al. (1980) found a choline-rich diet, given to mice, prevented the normal age-related decline in memory. However, the effect was only observed over a period of months and it is unclear whether the effect was due to enhanced cholinergic functioning rather than other mechanisms, such as changes in phopholipid metabolism.

Similarly, there is evidence that carnitine can offer benefits over the longer term. The question arises as to whether in the present study it was administered for a sufficient period and in a sufficient dose. Capriolli et al. (1990) are one of several groups who have given ALC to rats for 6–8 months and found a decrease in the characteristic age-related decline in memory. In the aged rat, chronic treatment with ALC has been found to improve brain morphology, for example reducing the loss of myelinated fibres, and decreasing the deposition of lipofuscin in the hippocampus and prefrontal cortex (Angelucci et al. 1986a, 1986b). In fact ALC, when given to ageing rats, decreases mortality (Markowska et al. 1990). Similarly there is an increasing number of reports that the administration of ALC, in doses of 1–2 g/day, for several months, improved memory and other aspects of cognition (Montgomery et al. 2003).

Again it is necessary to distinguish the possible short-term from long-term effects of administering carnitine. The studies mentioned previously examined long-term changes, there have been few attempts to consider the short-term impact of carnitine. A rare example was an electrophysiological study in which an intravenous injection of 20 mg/kg ALC influenced the P300 latency 40–80 min after injection (Nobilio et al. 1990). They argued that the effect of ALC on the P300 reflected cholinergic mechanisms. This study demonstrates that carnitine produces short-term changes in the brain's electrical activity, although the route of administration was different and the dose was higher than in the present study.

The finding that carnitine speeded decision times (Fig. 1) suggests that a dose of 500 mg for three days can influence cognitive functioning. This finding is of potential importance as Eysenck (1987) suggested that of the components that make up intelligence the most fundamental is mental speed. There have been repeated reports that better scores on intelligence tests are associated with quicker reaction times. However, the influence of carnitine on decision times should be viewed with some caution. Given the large number of statistical analyses that were carried out, and that there have been no previous studies of this or related topics, the possibility that the finding reflects a type-2 error cannot be excluded. There is a need to replicate the finding. The pattern of the finding, however, suggests that it may prove to be genuine. There were faster decisions with 1, 2, 4 and 8 lamps, a reflection of an overall improvement in processing speed. It is very much more likely that chance statistical findings would have resulted in faster processing with some, but not all lights.

The clearest finding from the present study is that the taking of a glucose-containing drink improved memory (Fig. 2), although unexpectedly this was not the case after consuming lecithin. Given the long-list of studies that have reported an association between the administration of glucose and better memory this finding was not surprising (see Introduction). That lecithin prevented the association between glucose provision and better memory was surprising and could not be readily explained.

In conclusion, it appears that the most robust phenomenon in this area is that raising blood glucose is associated with better memory. The present findings confirm the findings of many human and animal studies that the administration of glucose improves memory. Given the biochemical evidence, discussed above, that an increased supply of glucose is associated with an increased acetycholine synthesis, it was reasonable to hypothesise that an interaction between glucose and lecithin might result. Unfortunately this prediction was not confirmed. The evidence that the taking of carnitine and provision of glucose acted synergistically is a novel finding that should be further examined (Fig. 1). As carnitine is known to play an important role in the transport of the acetyl-Co A (Borum 1983), there is a plausible biochemical mechanism that might account for the finding.

The present finding must be kept in context. The dose of both lecithin and carnitine were lower and the duration of administration was shorter than in many previous studies of memory. The possibility that a synergistic action between carnitine and lecithin might occur with higher doses and longer term administration has not been

precluded by the present findings. When looking for a rapid enhancement of memory it would be better to look to approaches that manipulate the levels of blood glucose. Interesting there is a recent report that the glycaemic nature of carbohydrate-influenced memory in both humans and rats (Benton et al. 2003). The possibility that a sample of mild to moderately impaired elderly might prove more susceptible to such manipulations should also be considered.

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