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Effects of *Panax ginseng*, consumed with and without glucose, on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks

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Abstract

Single doses of the traditional herbal treatment *Panax ginseng* have recently been shown to lower blood glucose levels and elicit cognitive improvements in healthy, overnight-fasted volunteers. The specific mechanisms responsible for these effects are not known. However, cognitive improvements may be related to the glycaemic properties of *Panax ginseng*.

Using a double-blind, placebo-controlled, balanced-crossover design, 27 healthy young adults completed a 10 minute 'cognitive demand' test battery at baseline. They then consumed capsules containing either ginseng (extract G115) or a placebo and 30 minutes later a drink containing glucose or placebo. A further 30 minutes later (i.e. 60 minutes post-baseline/capsules) they completed the 'cognitive demand' battery six times in immediate succession. Depending on the condition to which the participant was allocated on that particular day, the combination of capsules/drink treatments corresponded to a dose of: 0 mg G115/0 mg glucose (placebo); 200 mg G115/0 mg glucose (ginseng); 0 mg G115/25 g glucose (glucose) or 200 mg G115/25 g glucose (ginseng/glucose combination). The 10 minute 'cognitive demand' battery comprised a Serial Threes subtraction task (2 min); a Serial Sevens subtraction task (2 min); a Rapid Visual Information Processing task (5 min); and a 'mental fatigue' visual analogue scale. Blood glucose levels were measured prior to the day's treatment, and before and after the post-dose completions of the battery.

The results showed that both *Panax ginseng* and glucose enhanced performance of a mental arithmetic task and ameliorated the increase in subjective feelings of mental fatigue experienced by participants during the later stages of the sustained, cognitively demanding task performance. Accuracy of performing the Rapid Visual Information Processing task (RVIP) was also improved following the glucose load. There was no evidence of a synergistic relationship between *Panax ginseng* and exogenous glucose ingestion on any cognitive outcome measure. *Panax ginseng* caused a reduction in blood glucose levels 1 hour following consumption when ingested without glucose.

These results confirm that *Panax ginseng* may possess gluco-regulatory properties and can enhance cognitive performance.

Keywords

Panax, ginseng, cognitive performance, acute, placebo, blood glucose, hypoglycaemia, healthy adults.

Introduction

The use of extracts of cultivated members of the Panax genus (ginseng) is documented as early as the first century (Hu, 1997) in the *Pen-ts'ao-ching of Shên-nung* (the divine plowman). Wild ginseng is also thought to have been in medicinal use for several thousand years before this time (Yun, 2001). Ginseng's traditional use is as a 'panacea' or whole body treatment. However, in the US it has previously been reported to be the most popular self-administered psychoactive herbal product (Barnes *et al*., 2004) with many consumers taking it to aid 'memory loss' and 'absent-mindedness' (see: Kennedy and Scholey, 2003). Despite an extensive literature documenting the effects of ginseng on potentially relevant physiological parameters, chronic administration of ginseng in humans has produced little evidence of behavioural effect. This lack of evidence of efficacy may be accounted for by

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the methodological shortcomings in the research. For instance, few human studies have used adequately standardized ginseng extracts, and many fail to adopt double blind or placebo controls (for reviews see: Vogler *et al*., 1999; Bahrke and Morgan, 1994, 2000; Kennedy and Scholey, 2003).

A recent series of placebo-controlled, double-blind, balanced-crossover studies has demonstrated modulation of cognitive performance following single doses of *Panax ginseng* (standardized extract G115) in young healthy humans. The most consistent finding is of improved memory performance following G115 alone (Kennedy *et al*., 2001a, 2002, 2004) and in combination with both *Ginkgo biloba* (Kennedy *et al*., 2001b, 2002) and guarana (*Paullinia cupana*) (Kennedy *et al*., 2004). Whilst these mnemonic effects appear to be robust, particularly following a single dose of 400 mg in one instance, both lower (200 mg) and higher (600 mg) doses led to significantly slower performance of attentional tasks (Kennedy *et al*., 2001b). Similarly, in the same cohort, whilst 400 mg improved accuracy of performing a serial subtraction task, 200 mg led to modest, but significant, reductions in the speed of performing the same task (Scholey and Kennedy, 2002). These decrements in the speed of task performance contrast with recent findings for the same 200 mg dose of improved speed of information retrieval, attention and arithmetical performance (Kennedy *et al*., 2004; Reay *et al*., 2005), and significantly shortened latency of the P300 component of auditory evoked potentials (Kennedy *et al*., 2003), and faster responses on an attentional task 90 minutes following 400 mg of G115 (Sünram-Lea *et al*., 2004).

The mechanisms by which ginseng might modulate human cognitive performance are not yet well understood, but they may involve several central and peripheral physiological effects that are potentially relevant to human cognitive performance. These include effects on the cardiovascular system, platelet aggregation, the Hypothalamic-Pituitary-Adrenal system, neurotransmission and nitric oxide synthesis (see: Kennedy and Scholey, 2003).

Ginseng extracts have also been shown to have gluco-regulatory properties. For instance, the long-term and acute hypoglycaemic effects of ginseng have been demonstrated both in rodents (Ohnishi *et al*., 1996; Xie *et al*., 2002) and humans (Sotaniemi *et al*., 1995; Tetsutani *et al*., 2000; Vuksan *et al*., 2000a, b, 2001). With regards to *Panax ginseng*, a reduction in fasted blood glucose levels and glycated haemoglobin were reported following 8 weeks' administration of 100 mg and 200 mg/day of an unspecified extract in 18 participants with type 2 Diabetes Mellitus (Sotaniemi *et al*., 1995). Similarly, Tetsutani *et al*. (2000) reported that 24 months of treatment with 3–4.5 g/day of Korean red *Panax ginseng* decreased HbA_{1c} (an index of average blood glucose levels over approximately the previous month) in 34 type 2 diabetics compared with controls. In the case of *Panax quinquefolius* (American ginseng), a decrease in fasted blood glucose and HbA_{1c}, has been reported in 24 type 2 diabetic patients following 8 weeks' administration of 1 g of a proprietary ginseng extract, taken 40 minutes before each meal (Vuksan *et al*., 2000b). The hypoglycaemic effects of single doses of *P. quinquefolius* have also been demonstrated, with reductions in blood glucose levels following a 25 g glucose challenge, during a 120 minute oral glucose tolerance test in both diabetic patients who had ingested 3 g, 6 g and 9 g (Vuksan *et al*., 2000a, b), and healthy participants administered 1 g, 2 g and 3 g of *P. quinquefolius* (Vuksan *et al*., 2000a, 2001).

It has previously been established that fluctuations in levels of circulating blood glucose can modulate cognitive performance. Cognitive impairment has been demonstrated as a result of both hypoglycaemia (Holmes *et al*., 1984; Gold *et al*., 1985) and lowered but supra-hypoglycaemic glucose levels (De Feo *et al*., 1988; Taylor and Rachman, 1988). Conversely, cognitive enhancement has been demonstrated across a wide variety of tasks following a glucose drink (Benton, 1990; Martin and Benton, 1999; Donohoe and Benton, 2000; Kennedy and Scholey, 2000; Scholey *et al*., 2001; Sünram-Lea *et al*., 2002). Other studies have reported a positive association between the rate at which a person's blood glucose levels fall, following an initial peak, and the level of cognitive performance, particularly during periods of cognitive demand (Scholey *et al*., 2001). It follows that any intervention which modulates glucose transport may also affect cognitive performance. There is some support for this notion from the finding that insulin administration can improve memory in sufferers from Alzheimer's disease (Watson and Craft, 2004).

Additionally, and of particular relevance to the present study, Reay *et al*. (2005) previously reported a placebo-controlled, double-blind, balanced-crossover study, that demonstrated that the administration of either 200 mg or 400 mg of *Panax ginseng* (G115) led to significant reductions in blood glucose levels, with concomitant speeded performance on a serial subtraction task and amelioration of mental fatigue following the 200 mg dose. Although this relationship between lowered blood glucose and raised cognitive performance was not expected, one explanation for such findings is that increased cellular uptake of blood glucose resulted in better performance and a concurrent fall in blood glucose levels. However, it should be noted that there was no correlation between change in cognitive performance and change in blood glucose following the treatments.

Given the above, it seems expedient to investigate the relationship between the administration of both glucose and ginseng on cognitive performance and blood glucose levels. Given that cognitively demanding tasks may be the most sensitive to glucose-related effects, the present placebo-controlled, double-blind, balanced-crossover study investigated the effects of single doses of: *Panax ginseng* (200 mg G115); glucose (25 g); and a combination of *Panax ginseng* and glucose (200 mg G115 + 25 g glucose) on blood glucose levels and cognitive performance during sustained 'mentally demanding' tasks.

Subjects and methods

Participants

Seventeen male and ten female undergraduate volunteers (mean age 21.89 years, S.D. 4.64) participated in the study, which was approved by the Northumbria University Division of Psychology Ethics committee and conducted in accordance with the Declaration of Helsinki. Prior to participation each participant gave

informed consent and completed a medical health questionnaire. All participants reported that they were in good health, and that they were free from heart disorders, high blood pressure, respiratory disorders, epilepsy, panic attacks and diabetes. Additionally, they reported being free from 'over-the-counter' treatments, illicit social drugs and prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. Heavy smokers (> 10 cigarettes/day) and pregnant females were excluded from the study. Of the 27 participants one was a light smoker (two per day), and this participant agreed to abstain from smoking on the days of testing. All participants were overnight fasted, were alcohol free for 12 hours prior to baseline measure, and abstained from products containing caffeine on the days of testing. Volunteers were paid £80 for their participation. Participants were randomly allocated a position on a Latin Square counterbalancing the treatment order by the computerised generation of random numbers.

The sample size employed was as per a previous study utilizing the same methodology (Reay *et al*., 2005), which in turn was arrived at via a power calculation.

Blood glucose measurement

Blood glucose levels were monitored using a Reflotron Plus diagnostic machine and test sticks (Roche Diagnostics, Germany). The reliability of the test has previously been confirmed (Price and Koller, 1988).

On each of the four study days, blood glucose levels were measured via capillary finger prick at baseline, 1 hour post-treatment (before commencement of the first post-dose battery completion), and after the sixth (i.e. end of testing) completion of the demand battery.

Cognitive demand battery

A 10 minute, computerized 'cognitive demand battery' comprizing the Serial Threes subtraction task (2 mins), Serial Sevens subtraction task (2 mins), a Rapid Visual Information Processing task (RVIP – 5 mins), and a 'mental fatigue' visual analogue scale, was utilized. Tasks within this battery have been shown to be sensitive to the effects of *Ginkgo biloba* and *Panax ginseng* (Scholey and Kennedy, 2002), and a glucose drink (Scholey *et al*., 2001). The overall experimental paradigm has been used to demonstrate positive effects of a caffeine/glucose energy drink (Kennedy and Scholey, 2004) and *Panax ginseng* (Reay *et al*., 2005). The individual tasks are described below.

Serial Sevens A modified computerized version of the Serial Sevens test was utilized. The original verbal Serial Sevens test (Hayman, 1942) has appeared in a number of forms, including as part of the Mini-Mental State Examination for dementia screening (Folstein *et al*., 1975). It has been used to assess cognitive impairment during hypoglycaemia (Hale *et al*., 1982; Taylor and Rachman 1988), and has also been used to investigate the relationship between blood glucose levels and cognitive performance (Kennedy and Scholey, 2000; Scholey *et al*., 2001; Scholey, 2001) and the acute effects of ginkgo and ginseng (Scholey and Kennedy, 2002). In the current study, computerized versions of serial subtraction tasks were implemented (see Scholey *et al*., 2001 for details), using tests of 2 mins duration. For the Serial Sevens task a standard instruction screen informed the participant to count backwards in sevens from the given number, as quickly and accurately as possible, using the keyboard's linear number pad to enter each response. Participants were also instructed verbally that if they were to make a mistake they should carry on subtracting from the new incorrect number. A random starting number between 800 and 999 was presented on the computer screen, which was cleared by the entry of the first response. Each three-digit response was entered via the numeric keypad with each digit being represented on screen by an asterisk. Pressing the enter key signalled the end of each response and cleared the three asterisks from the screen. The task was scored for total number of subtractions and number of errors. In the case of incorrect responses, subsequent responses were scored as positive if they were correct in relation to the new number.

Serial Threes The Serial Threes task was identical to Serial Sevens, except that it involved serial subtraction of threes.

Rapid Visual Information Processing task (RVIP) This task has been widely used to study the cognitive effects of psychotropic drugs, and has been shown to be sensitive to augmented blood glucose levels (Donohoe and Benton, 1999). The participant monitors a continuous series of digits for targets of three consecutive odd or three consecutive even digits. The digits are presented on the computer screen at the rate of 100 per minute in pseudo-random order and the participant responds to the detection of a target string by pressing the space bar as quickly as possible. The task is continuous and lasts for 5 minutes, with eight correct target strings being presented in each minute. The task is scored for number of target strings correctly detected, average reaction time for correct detections and number of false alarms.

'Mental fatigue' visual analogue scale Participants rated their subjective feelings of mental fatigue on a 100 mm visual analogue scale with the left and right end-points labelled 'not at all' and 'very much so' respectively.

Treatments

Ginseng capsule treatment Active treatments and placebo capsules, matched for size, colour, opacity and odour were provided by the manufacturer. The individual capsules contained either an inert placebo, or 100 mg of *Panax ginseng* extract (G115, Pharmaton SA, Lugano, Switzerland).

Glucose drink treatment Active treatments and placebo drinks, matched for sweetness, volume (180 ml of tap water and 20 ml of a sugar-free fruit cordial drink), odour and colour were mixed in the laboratory on each day of testing. The individual drinks contained either 25 g of glucose or 30 mg of saccharin.

Treatment preparation and administration Prior to the commencement of the study, a disinterested third party, who had no other involvement in the study, prepared the capsule treatments for each of the individual participants (in accordance with the study's Latin Square) and sealed them in containers marked only with the participant code and study day number. The same third party prepared the glucose and placebo drinks for each participant (in accordance with the study's Latin Square) on the morning of each study day. Depending on the condition to which the participant was allocated on that particular day, the combination of capsules and drink corresponded to a dose of: 0 mg G115/0 mg glucose (placebo); 200 mg G115/0 mg glucose (ginseng); 0 mg G115/25 g glucose (glucose) or 200 mg G115/25 g glucose (ginseng/glucose combination).

Procedure

Each participant was required to attend a practice day and 4 active study days that were conducted not less than 7 days apart to ensure a sufficient washout period between conditions. Testing took place in a suite of research-dedicated laboratories with participants visually isolated from each other.

On arrival on the practice day, participants were randomly allocated to a treatment regimen according to a Latin Square that counterbalanced the order of treatments across the 4 active days of the study.

The practice day was identical to the 4 study days with the exception that no treatment was offered, nor analysis of the resulting data undertaken.

On the 4 remaining study days (testing commencing at 9.00 AM after an overnight fast), after an initial practice run through the 10-minute 'cognitive demand battery' (Serial Threes – 2 mins, Serial Sevens – 2 mins, RVIP – 5 mins, Mental fatigue rating scale) on arriving at the laboratory (data not analysed), each participant completed the 10-minute cognitive demand battery pre-dose, followed immediately by ingestion of either 200 mg G115 or placebo capsules. This in turn was followed 30 minutes later by the ingestion of a 200 ml drink which had dissolved within it either 25 g of glucose or a saccharine placebo. Thus, the participants received one of the following treatments: 0 mg G115/0 mg glucose (placebo); 200 mg G115/0 mg glucose (ginseng); 0 mg G115/25 g glucose (glucose) or 200 mg G115/25 g glucose (ginseng/glucose combination). Commencing 30 minutes after consuming the day's drink treatment the participants completed the demand battery six times in succession (i.e. a total of 60 minutes of continuous task performance). Participant's blood glucose levels were measured pre-dose, 1 hour post-dose (i.e. before commencing the cognitive tasks), and after the six completions of the 'cognitive demand battery'.

Statistics

'Change from baseline' scores on the serial subtractions, RVIP, subjective mental fatigue and blood glucose levels were analysed using the Minitab statistical package version 13.1. Following an initial repeated measures ANOVA (ginseng × glucose × demand battery completion [or time of blood sample]) conducted to determine main and interaction effects, planned comparisons were made at each time point utilizing t tests with MSError as an error term (Keppel, 1991). In the case of blood glucose measurements, individual a priori comparisons were made between administration of glucose plus and minus ginseng, and administration of the glucose placebo plus and minus ginseng. For the cognitive and mood measures comparisons were made between placebo (0 mg G115/0 g glucose) and each of the active treatments. To ensure the overall protection level, comparisons were strictly planned prior to commencement of the study, only probabilities associated with planned comparisons were calculated, and all testing was two-tailed.

Post hoc *correlation analysis* Pearson's Product-Moment Correlation Coefficients were carried out to investigate any relationship between cognitive performance and blood glucose levels. 'Change from baseline' blood glucose levels at pre-test and the end of testing were correlated with 'change from baseline' task performance at the nearest post-dose completion of the demand battery (i.e. the first and sixth completions respectively). Correlations were conducted separately for each condition.

Results

Baseline scores

Prior to analysis of change from baseline data, raw baseline scores for all four conditions (placebo, ginseng, glucose and ginseng/glucose combination) for each of the primary outcome measures (blood glucose levels, mental fatigue, RVIP, Serial Threes and Serial Sevens) were subject to one way repeated measures ANOVAs (participant × treatment). There were no significant differences in baseline performance on any measures. Mean pre-dose baseline raw scores and change from baseline scores, for each condition at each post-dose time point on blood glucose levels and the individual cognitive tasks, are presented in Table 1.

Blood glucose levels

The initial repeated measure ANOVA (ginseng × glucose × time of blood sample) revealed a significant interaction between administration of glucose and time of blood sample [$F(1,26) = 104.52$, $P < 0.001$]. Planned comparisons, comparing each treatment to placebo at each time point, revealed that the ingestion of a 25 g glucose load alone [$t(26) = 9.40$, $P < 0.001$] or in combination with 200 mg ginseng [$t(26) = 10.570$, $P < 0.001$] led to significantly increased blood glucose levels at the 1 hour post-dose measurement point. However, following the ingestion of ginseng alone, blood glucose levels were significantly reduced at the 1 hour post-dose measurement point [$t(26) = 2.096$, $P = 0.046$] (Fig. 1).

The ANOVA also revealed a significant interaction between administration of glucose and ginseng [$F(1,26) = 5.26$, $P = 0.03$] on blood glucose levels (Fig. 2). Taken across the two post-dose sessions the pattern of blood glucose modulation following the

Table 1 Effects of 200 mg G115, 25 g glucose, 200 mg/25 g ginseng/glucose combination, and placebo, on task performance and blood glucose levels. Mean baseline performance score/glucose level and mean change from baseline performance score/glucose level at each post-dose battery completion point/glucose measurement point, with standard errors in italics. Significance (planned comparisons) is indicated in bold type ([A] $p<0.05$; [B] $p<0.01$; [C] $p<0.005$; [D] $p<0.001$; [E] $p<0.0005$)

			Post-dose change from baseline score											
Measure	Pre-dose baseline score		1		2		3		4		5		6	
Mental fatigue (mm)														
Placebo	26.296	*3.380*	0.296	*1.671*	7.296	*2.663*	13.481	*3.233*	18.481	*4.134*	27.444	*4.683*	33.889	*5.531*
200 mg	25.889	*3.687*	0.222	*1.825*	6.296	*2.179*	13.889	*2.883*	18.333	*3.512*	**22.519**[B]	*3.270*	**26.926**[D]	*3.737*
Glucose (25 g)	27.778	*3.794*	1.333	*1.974*	7.000	*2.473*	14.481	*3.413*	18.630	*3.842*	**23.148**[A]	*3.921*	**28.259**[C]	*4.372*
Combination	25.778	*3.237*	2.778	*3.021*	9.593	*2.833*	16.111	*3.099*	21.000	*3.267*	27.852	*4.130*	33.148	*4.099*
RVIP reaction time (sec)														
Placebo	0.533	*0.014*	0.008	*0.008*	0.012	*0.009*	0.006	*0.014*	0.016	*0.018*	0.009	*0.014*	−0.006	*0.011*
200 mg	0.530	*0.020*	0.008	*0.015*	0.025	*0.013*	−0.019	*0.010*	**0.021**[B]	*0.014*	0.005	*0.014*	0.018	*0.015*
Glucose (25 g)	0.519	*0.018*	0.014	*0.012*	**0.023**[A]	*0.010*	0.009	*0.010*	0.018	*0.009*	0.009	*0.012*	0.007	*0.012*
Combination	0.535	*0.016*	0.012	*0.013*	**0.017**[A]	*0.014*	0.016	*0.017*	0.011	*0.013*	−0.001	*0.009*	−0.009	*0.013*
RVIP (false alarms)														
Placebo	2.407	*0.920*	0.000	*0.358*	1.852	*0.860*	0.926	*0.792*	0.704	*0.762*	0.519	*0.684*	3.556	*2.878*
200 mg	2.889	*1.023*	0.148	*0.395*	0.407	*0.382*	1.519	*0.543*	1.148	*0.533*	0.926	*0.503*	**0.963**[C]	*0.801*
Glucose (25 g)	4.593	*1.753*	1.111	*0.783*	**0.667**[A]	*0.669*	**1.185**[A]	*0.618*	−0.704	*0.449*	−0.741	*0.584*	**−1.259**[E]	*1.209*
Combination	3.407	*1.386*	0.222	*0.390*	**0.667**[A]	*0.381*	−0.074	*0.783*	0.444	*0.892*	0.259	*0.780*	**0.222**[E]	*0.715*
Serial 3s (total responses)														
Placebo	41.037	*2.070*	0.222	*1.040*	1.704	*1.083*	0.000	*1.345*	−0.704	*1.294*	−0.148	*1.313*	−0.481	*0.992*
200 mg	40.074	*2.362*	1.963	*1.205*	3.259	*1.273*	**2.704**[A]	*1.223*	**2.185**[A]	*1.402*	2.000	*1.314*	**3.407**[C]	*2.255*
Glucose (25 g)	40.222	*2.629*	0.778	*1.951*	1.000	*1.578*	**3.481**[B]	*1.502*	**3.667**[D]	*1.273*	2.259	*2.143*	**2.333**[A]	*1.844*
Combination	40.259	*2.645*	1.000	*0.887*	0.630	*1.378*	0.889	*1.181*	−0.037	*1.825*	−0.111	*1.889*	−1.556	*1.803*
Serial 3s (errors)														
Placebo	1.500	*0.255*	0.111	*0.454*	0.222	*0.566*	0.111	*0.308*	0.259	*0.380*	0.741	*0.485*	0.556	*0.408*
200 mg	1.241	*0.210*	0.778	*0.435*	0.148	*0.260*	0.630	*0.457*	0.519	*0.274*	−0.037	*0.340*	0.185	*0.311*
Glucose (25 g)	2.304	*0.255*	0.444	*0.351*	0.296	*0.413*	−0.259	*0.511*	0.037	*0.513*	**−0.593**[A]	*0.553*	−0.185	*0.490*
Combination	1.714	*0.337*	0.148	*0.426*	0.037	*0.442*	−0.296	*0.440*	**1.481**[A]	*1.436*	0.111	*0.516*	0.926	*0.487*
Serial 7s (total responses)														
Placebo	25.704	*1.630*	1.778	*0.790*	0.000	*0.801*	0.185	*0.967*	1.852	*0.910*	1.630	*0.744*	1.815	*0.974*
200 mg	25.963	*2.182*	0.444	*0.752*	1.148	*0.938*	1.519	*0.881*	2.037	*0.914*	1.370	*0.994*	2.259	*0.919*
Glucose (25 g)	26.222	*2.091*	**0.370**[A]	*0.911*	0.074	*0.811*	1.889	*0.725*	0.556	*0.930*	1.407	*1.246*	1.963	*0.944*
Combination	25.444	*2.021*	**0.926**[B]	*0.792*	0.074	*0.808*	2.000	*0.887*	2.185	*1.041*	2.481	*0.902*	2.778	*0.959*
Serial 7s (errors)														
Placebo	1.704	*0.301*	0.444	*0.431*	0.222	*0.375*	0.296	*0.406*	0.370	*0.404*	0.407	*0.411*	1.000	*0.406*
200 mg	1.852	*0.412*	0.222	*0.535*	0.185	*0.437*	0.148	*0.503*	0.111	*0.466*	0.296	*0.562*	**0.074**[A]	*0.456*
Glucose (25 g)	1.593	*0.240*	0.444	*0.411*	0.370	*0.431*	0.667	*0.406*	0.148	*0.409*	0.556	*0.289*	**0.000**[A]	*0.406*
Combination	1.667	*0.250*	0.000	*0.325*	0.111	*0.355*	0.185	*0.346*	0.593	*0.478*	0.185	*0.396*	**0.000**[A]	*0.405*
Blood glucose levels (mmol/litre)	*Pre-dose* baseline score		*60 mins* post										*120 mins* post	
Placebo	5.229	*0.125*	0.198	*0.126*									−0.721	*0.114*
200 mg	5.462	*0.112*	**0.630**[A]	*0.096*									−0.708	*0.121*
Glucose (25 g)	5.338	*0.153*	**1.739**[E]	*0.206*									−0.923	*0.156*
Combination	5.077	*0.122*	**1.980**[E]	*0.268*									−0.603	*0.151*

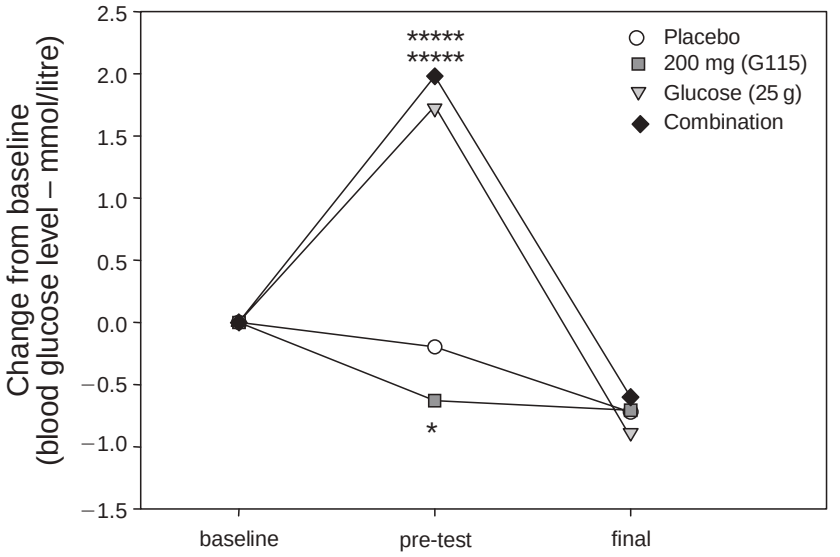

Figure 1 Effects of 200 mg G115, 25 g glucose, 200 mg/25 g ginseng/glucose combination, and placebo, on blood glucose levels. Figure depicts mean change from baseline glucose level at 1 hour post-treatment (pre-test) and after six (final) post-dose completions of the battery (* $p<0.05$; ***** $p<0.0005$)

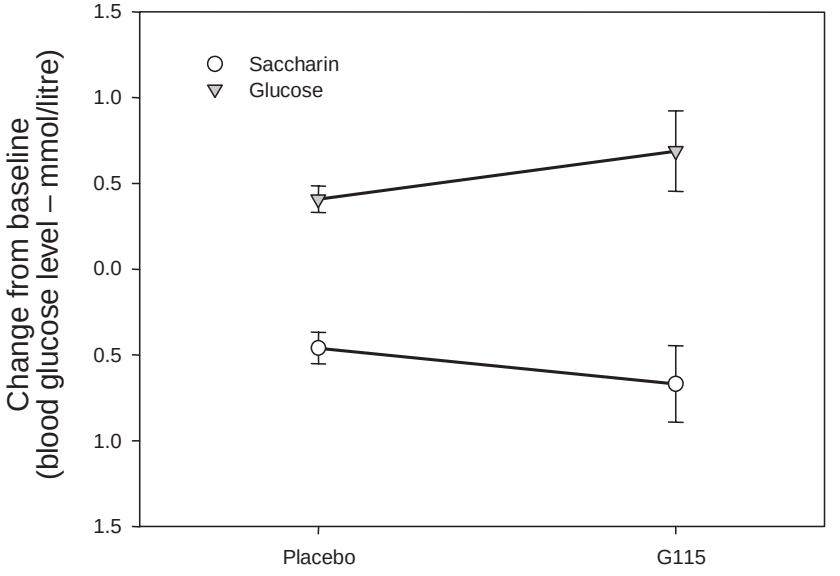

Figure 2 Post-dose interaction between ginseng and glucose on blood glucose levels (mean change from baseline values across both post-dose measurements)

administration of ginseng was for an increase in circulating blood glucose levels in the presence of the 25 g glucose load but a reduction in blood glucose levels in the absence of the glucose load (although it should be noted that *post hoc* comparisons of the effects of ginseng within the glucose/placebo conditions were non-significant in themselves).

Serial Threes subtractions

The repeated measures ANOVA (ginseng × glucose × demand battery completion) revealed a significant interaction between the administration of glucose and ginseng on the total number of Serial Threes subtractions made [$F(1,130)=4.52$, $P=0.043$]. Planned comparisons comparing each treatment to placebo at each demand battery completion revealed significantly more Serial Threes subtractions were performed following 200 mg G115 alone (ginseng condition) at the third [$t(130)=2.088$, $P=0.039$], fourth [$t(130)=2.231$, $P=0.027$] and sixth [$t(130)=3.004$, $P=0.003$] demand battery completions. Similarly, following a 25 g glucose load alone (glucose condition) participants produced significantly more Serial Threes subtractions on the third [$t(130)=2.689$, $P=0.008$], fourth [$t(130)=3.376$, $P=0.001$] and sixth [$t(130)=2.174$, $P=0.032$] demand battery completions (Fig. 3).

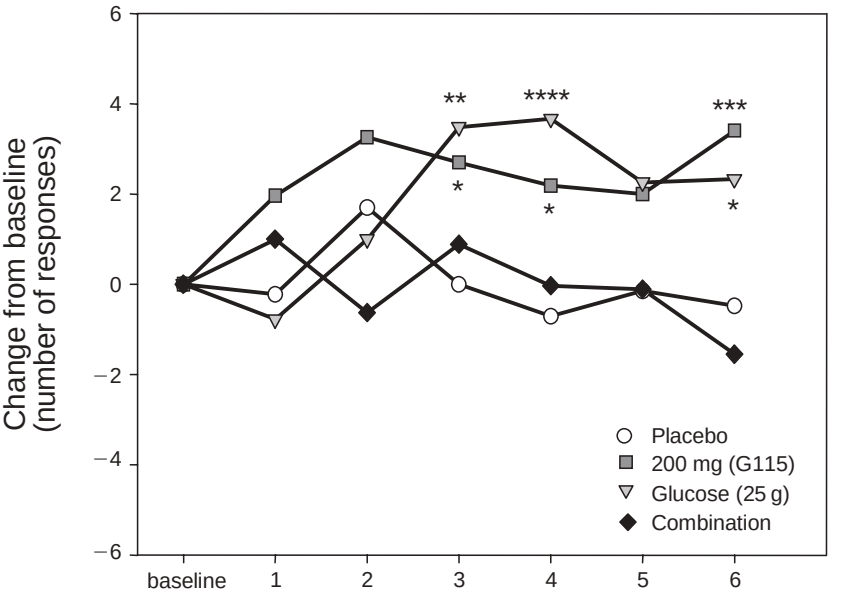

Figure 3 Effects of 200 mg G115, 25 g glucose, 200 mg/25 g ginseng/glucose combination, and placebo, on the number of Serial Threes subtractions performed. Figure depicts mean change from baseline scores at each post-dose completion (one to six) of the battery (* $p<0.05$; *** $p<0.005$; **** $p<0.001$)

Serial Sevens subtractions

No significant results were revealed.

Rapid Visual Information Processing task (RVIP)

The initial ANOVA (ginseng × glucose × demand battery completion) revealed a significant main effect of glucose administration [$F(1,130)=7.72$, $P=0.01$] on the number of false alarms participants committed during the RVIP task. There were significantly fewer false alarms committed following a glucose load, irrespective of ginseng administration. Planned comparisons comparing each treatment to placebo at each demand battery completion revealed a significant reduction in the number of false alarms following a 25 g glucose load alone (glucose condition) on the second [$t(130)=2.804$, $P=0.006$] third [$t(130)=2.35$, $P=0.020$] and sixth [$t(130)=5.361$, $P=0.0000004$] demand battery completions. Additionally, a reduction in the number of false alarms was revealed following a glucose load combined with 200 mg G115 on the second [$t(130)=2.804$, $P=0.006$] and sixth [$t(130)=3.711$, $P=0.0003$] demand battery completion. A single significant reduction in the number of false alarms was also revealed following 200 mg G115 alone (ginseng condition) on the sixth [$t(130)=2.887$, $P=0.005$] completion of the demand battery only (Fig. 4).

Mental fatigue

Planned comparisons comparing each treatment to placebo at each demand battery completion revealed a significant amelioration in subjective ratings of mental fatigue following a 25 g glucose load alone (glucose condition) on the fifth [$t(130)=2.179$, $P=0.031$] and sixth [$t(130)=2.855$, $P=0.005$] completions of the demand battery. Similarly, a significant amelioration in subjective ratings of mental fatigue were revealed following 200 mg G115 alone (ginseng condition) on the fifth [$t(130)=2.498$, $P=0.014$] and sixth [$t(130)=3.531$, $P=0.001$] completions of the demand battery (Fig. 5). There was no effect of the combined treatments.

Post hoc correlation analysis

The *post hoc* correlations revealed no interpretable significant relationships between cognitive performance and blood glucose levels.

Discussion

The present study was designed to investigate the effects of *Panax ginseng* on cognitive performance, mood and blood glucose levels, both in the presence and absence of exogenously raised blood glucose levels (via administration of a 25 g glucose load 30 minutes post-dose). More specifically, it was intended to address the suggestion that ginseng's acute positive effects on human cognition may be explained, at least in part, through its potential promotion of the cellular uptake of glucose. The methodology employed also allowed an examination of the effect of each individual treatment (200 mg G115 and a 25 g glucose load) in isolation, in comparison to placebo, on each of the primary outcome measures.

The results revealed no synergistic relationship between *Panax ginseng* (200 mg G115) and a 25 g glucose load on any of the primary cognitive outcome measures. The results, however, did reveal that single doses of either *Panax ginseng* (200 mg G115) or a 25 g glucose load can modulate circulating blood glucose levels, enhance cognitive performance of a mental arithmetic task (Serial

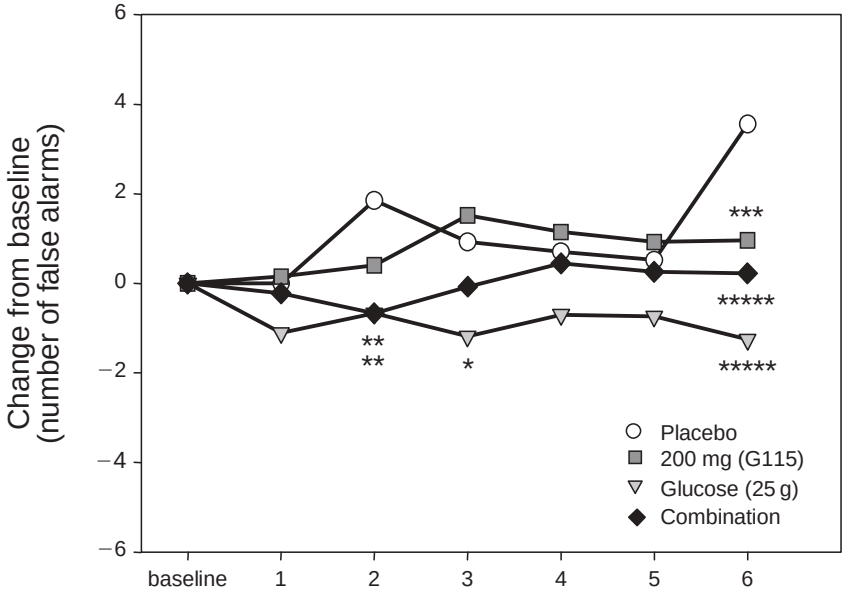

Figure 4 Effects of 200 mg G115, 25 g glucose, 200 mg/25 g ginseng/glucose combination, and placebo, on the number of False alarms committed for the RVIP task. Figure depicts mean change from baseline scores at each post-dose completion (one to six) of the battery (* $p<0.05$; ** $p<0.01$; *** $p<0.005$; ***** $p<0.0005$)

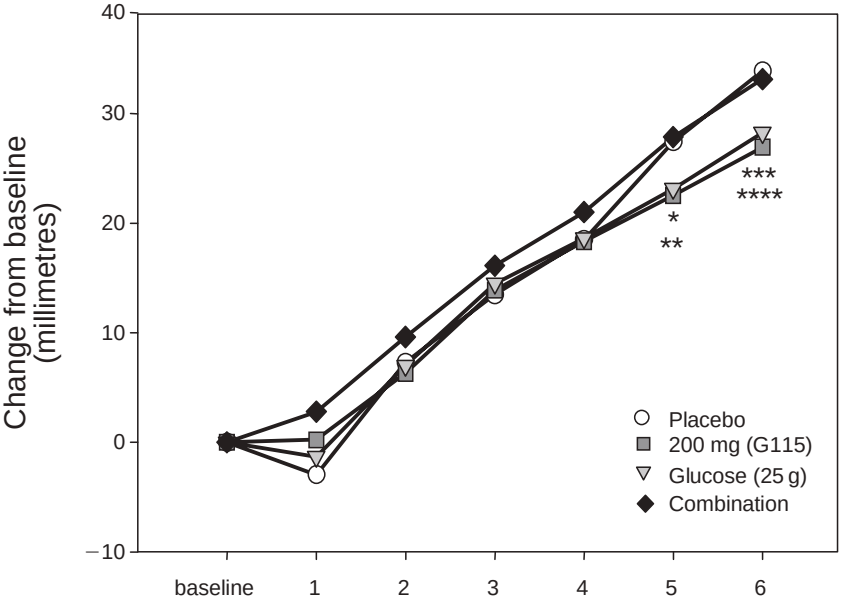

Figure 5 Effects of 200 mg G115, 25 g glucose, 200 mg/25 g ginseng/glucose combination, and placebo, on the participants' subjective ratings of mental fatigue. Figure depicts mean change from baseline scores at each post-dose completion (lower scores indicate reduced mental fatigue) (* $p<0.05$; ** $p<0.01$; *** $p<0.005$; **** $p<0.001$)

Threes) and ameliorate the increase in subjective feelings of mental fatigue experienced by participants during sustained intense cognitive processing. Accuracy of performing the Rapid Visual Information Processing task (RVIP) was also improved following the 25 g glucose load.

In relation to blood glucose levels, the results confirmed the absorption of glucose into the blood stream following a 25 g glucose load, and also revealed a significant interaction between the administration of ginseng and glucose (Fig. 2) indicative of *Panax ginseng*'s glucose modulating properties. The pattern of results showed that, in the absence of a glucose load (i.e. in overnight-fasted participants) a single dose of *Panax ginseng* (200 mg G115) resulted in a significant post-dose fall in circulating blood glucose levels at the assessment 1 hour following the ingestion of ginseng. There was also a significant interaction between the consumption of ginseng and glucose levels assessed across both post-dose assessments (Fig. 2). This interaction reflected a pattern of increased glucose levels when ginseng was taken with

glucose, and reduced glucose levels when ginseng was taken with placebo (i.e. in a fasted state). It should be noted, however, that the individual *post hoc* comparison of means for the ginseng and placebo groups while in the glucose drink condition did not show a specific significant increase associated with ginseng per se.

Research has previously addressed the chronic effects of both *Panax ginseng* (Sotaniemi *et al*., 1995; Vuksan *et al*., 2000) and *Panax quinquefolius* (Tetsutani *et al*., 2000) and the acute effects of the latter on the glycaemic response to a glucose challenge (Vuksan *et al*., 2000b, 2001; Sievenpiper *et al*., 2003a). Most pertinently the results of the present study are consistent with those of Reay *et al*. (2005) who demonstrated that the ingestion of either a single dose of 200 mg or 400 mg of *Panax ginseng* (G115) led to a significant reduction in circulating blood glucose levels in a cohort of young, healthy, overnight-fasted volunteers. In the case of the current study, planned comparisons confirmed Reay *et al*.'s (2005) finding that *Panax ginseng* lead to a reduction in blood glucose levels 1 hour post-dose in the absence of a glucose load.

The pattern of differential modulation of blood glucose levels following *Panax ginseng* with and without a glucose load is not out of line with previous research that demonstrated an increase in blood glucose levels during a 120 minute oral glucose tolerance test (75 g), using data pooled from five different doses of powdered *Panax ginseng* root (Sievenpiper *et al*., 2003b). Interestingly, Sievenpiper *et al*. (2004) reported that an extract of *Panax ginseng*, but not eight other ginseng extracts (*Sanchi*, *Siberian*, *American*, *Asian*, *Korean red*, *Japanese*, *wild American*, and *Vietnamese*) was associated with an increase in blood glucose levels and a greater insulin response following a glucose load. Taken with the evidence of opposite effects for *Panax quinquefolius* following a glucose load in diabetic and healthy participants (Vuksan *et al*., 2000a, 2000b, 2001), these results suggest that the differential effects of these extracts and members of the *Panax* genus require further investigation.

With regards cognitive performance on the serial subtraction tasks, whilst the initial ANOVA of the Serial Sevens data revealed a trend ($P = 0.07$) towards a treatment effect on the total number of subtractions performed, the only significant results on the ANOVA were obtained for the Serial Threes task. This initial analysis revealed a significant interaction between ginseng and glucose administration for the total number of Serial Threes subtractions performed. Planned comparisons revealed that 200 mg G115 led to a significantly greater number of Serial Threes subtractions being performed at the third, fourth and fifth completions of the demand battery. Similarly a greater number of Serial Threes subtractions were performed at the third, fourth and sixth completions of the demand battery following a 25 g glucose load. There was no effect of combining 200 mg with a 25 g glucose load at any time point (Fig. 3). This improved speed of performance, for both ginseng and glucose conditions, was not associated with greater production of errors, precluding the possibility of any treatment specific 'speed/accuracy trade-off'.

The improved Serial Threes performance following both single treatments is generally in line with previous demonstrations of working memory task enhancement by glucose (e.g. Martin and Benton, 1999; Sünram-Lea *et al*., 2002) and recent findings of faster memory, attention (Kennedy *et al*., 2004) and Serial subtraction task performance (Kennedy *et al*., 2004; Reay *et al*., 2005) and decreased latency of the P300 component of auditory evoked potentials (Kennedy *et al*., 2003) following *Panax ginseng*. However, they are somewhat at odds with previous reports of the enhancement of serial subtraction performance being restricted to the more 'mentally demanding' Serial Sevens task following both 200 mg G115 (Reay *et al*., 2005) and a 25 g glucose load (Kennedy and Scholey, 2000; Scholey *et al*., 2001). Reference to the planned comparisons for the Serial Sevens task (which are not reported due to a lack of significance on the initial ANOVA) does, however, show that both glucose alone and glucose combined with ginseng led to a significant increase in speed of performance that was restricted to the first completion of the Serial Sevens. This is entirely in keeping with the previous studies (Kennedy and Scholey, 2000; Scholey *et al*., 2001), both of which involved a single completion of these tasks. This also tends to suggest that the pattern of results evinced here might be related to the different demand characteristics of the multiple completions of these tasks, with the benefits of both glucose and ginseng only becoming apparent as fatigue (or another unidentified factor) increased with repeated performance of the Serial Threes task. With regards ginseng the discrepancy in results here in comparison to Reay *et al*. (2005) may well also be due to minor differences in the levels of single ginsenosides, or groups of ginsenosides (e.g. the ratio of panaxadiols to panaxatriols) contained in an extract that is standardized to total per cent content of ginsenosides.

For the RVIP task the initial ANOVA revealed a significant main effect of glucose administration on the number of false alarms committed. There were significantly fewer false alarms committed following the 25 g glucose drink, irrespective of ginseng administration. Planned comparisons revealed that significantly fewer false alarms were committed on the second, third and sixth demand battery completions for the glucose condition. Similarly, significantly fewer false alarms were committed on the second and sixth demand battery completions for the ginseng and glucose combination condition (Fig. 4). Accuracy in performing the RVIP task has previously been shown to be improved following a glucose-caffeine energy drink using the same experimental protocol and demand battery as used in the present study (Kennedy and Scholey, 2004).

In relation to the reported subjective feelings of mental fatigue it was found that both 200 mg G115 and a 25 g glucose load administered in isolation led to a significant amelioration in the participants' subjective feelings of mental fatigue towards the end of testings. The result (Fig. 5) of the present study are consistent with that of Reay *et al*. (2005) who reported that both 200 mg and 400 mg of *Panax ginseng* led to a significant amelioration of participants' subjective ratings of the mental fatigue associated with an extended period of intense cognitive processing.

The mechanisms responsible either for ginseng's glycaemic effect or its cognitive effects are not clear at present. With regards the former, Vuksan *et al*. (2000a) suggested three possible mechanisms that could account for modulation in blood glucose levels. These include the modulation of glucose disposal, glucose

transport or insulin secretion. The latter two may well be mediated by increased nitric oxide (NO) production (Roy *et al*., 1998; Spinas *et al*., 1998). The involvement of ginsenosides in this proposed mechanism is supported by the results of a number of studies. For example, 8 weeks' administration of American ginseng in type 2 diabetics led to an increase in NO concentration which correlated with improvements observed in HbA_{1c} (Xu *et al*., 2000; see also: Reay *et al*. 2005).

In a previous paper we speculatively suggested that *Panax ginseng* may promote the transport of glucose, by an unknown mechanism, into active cells (i.e. leading to a reduction in circulating blood glucose levels) and thus facilitating metabolism in task-sensitive structures (i.e. leading to improved behavioural performance) (see: Reay *et al*., 2005). The present study provides no support for such a hypothesis; for example, there were no behavioural improvements or reductions in blood glucose levels revealed following the combination treatment. However, for the second time, *Panax ginseng* did lead to improved behavioural performance and concomitant reductions in blood glucose levels when ingested by participants in a fasted state. Therefore, it still remains possible that ginseng exerts its beneficial cognition enhancing effects via some unknown gluco-regulatory mechanism. It should be noted that there was no direct correlation between the fall in blood glucose levels and performance.

Whilst the current study utilized participants in an overnight-fasted state, and provided increased glucose levels by administering a glucose drink in order to provide adequate experimental control of their gluco-regulatory state, it has to be conceded that this is not necessarily the normal dietary state of the majority of consumers at the time that they consume ginseng. Future research might well be directed towards the effects of ginseng in cohorts in their normal dietary state. This having been said, the current research study does reinforce the potential importance of this line of research with regards treatments for diabetes. Vuksan *et al*. (2001) has suggested that *Panax quinquefolius* may be an effective alternative therapy for patients suffering from type 2 diabetes. However, it should be noted that *Panax quinquefolius* is one of the less commonly used members of the *Panax* genus, whereas *Panax ginseng* is notable for its global ubiquity.

Whilst its potential utility in the treatment of conditions that feature disturbed gluco-regulation is of great interest, the present findings suggest that *Panax ginseng* (G115) may have opposite effects when administered in the absence or presence of glucose. Further research is required to delineate the mechanisms underlying the demonstrated gluco-regulatory effects and whether these effects represent a net benefit or cost to consumers.

In conclusion, 1 hour following administration of *Panax ginseng* blood glucose levels were reduced in fasted individuals, with an overall pattern of blood glucose modulation that suggested an opposite effect when administered before exogenous glucose. Both *Panax ginseng* and glucose, when administered in isolation of each other, led to improved task performance, and reduced mental fatigue as a consequence of extended task performance. These latter effects were not directly related to the modulation of blood glucose levels. Given the potential utility of a treatment that beneficially modulates blood glucose levels whilst concomitantly enhancing cognitive performance, the mechanisms underlying these effects require further investigation.

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