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Single doses of Panax ginseng (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity

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Abstract

Single doses of the traditional herbal treatment *Panax ginseng* have recently been shown to elicit cognitive improvements in healthy young volunteers. The mechanisms by which ginseng improves cognitive performance are not known. However, they may be related to the glycaemic properties of some Panax species. Using a double-blind, placebo-controlled, balanced crossover design, 30 healthy young adults completed a 10 min test battery at baseline, and then six times in immediate succession commencing 60 min after the day's treatment (placebo, 200 mg G115 or 400 mg G115). The 10 min battery comprised a Serial Threes subtraction task (2 min); a Serial Sevens task (2 min); a Rapid Visual Information Processing task (5 min); then a 'mental fatigue' visual analogue scale. Blood glucose was measured prior to each day's treatment, and before, during and after the post-dose completions of the battery. Both the 200 mg and 400 mg treatments led to significant reductions in blood glucose levels at all three post-treatment measurements ($p < 0.005$ in all cases). The most notable behavioural effects were associated with 200 mg of ginseng and included significantly improved Serial Sevens subtraction task performance and significantly reduced subjective mental fatigue throughout all (with the exception of one time point in each case) of the post-dose completions of the 10 min battery ($p < 0.05$). Overall these data suggest that *Panax ginseng* can improve performance and subjective feelings of mental fatigue during sustained mental activity. This effect may be related to the acute gluco-regulatory properties of the extract.

Keywords

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

Introduction

Ginseng (species of the genus Panax) products are amongst the most popular self-administered herbal products for 'memory loss' and 'absentmindedness'(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 benefits. This lack of evidence of efficacy may be accounted for by the methodological shortcomings. For instance, few studies into the effects of ginseng in humans have used adequately standardized ginseng extracts, and many fail to adopt double-blind or placebo controls (Bahrke and Morgan, 1994, 2000; Vogler *et al.*, 1999; Kennedy and Scholey, 2003). As a recent example, Persson *et al.* (2004) reported a lack of positive behavioural effects of ginseng in a group who self-reported taking the extract either for over two years or an average of six months. However, the study used too small a sample for their chosen statistical analysis, utilized non-standardized psychometric instruments, no placebo, and made no attempt to standardize either extract or dosing regime (see Scholey *et al.*, 2005a).

However, a recent series of placebo-controlled, double-blind, balanced crossover studies has identified both positive, and to a lesser extent, negative, cognitive and mood effects of acute doses of *P. 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

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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.*, 2001a). 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 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), and significantly shortened latency of the P300 component of auditory evoked potentials (Kennedy *et al.*, 2003), and following 400 mg G115, faster responses on an attentional task 90 min post-dose (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).

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, c, 2001a). With regards *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 (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. With regards *Panax quinquefolius* (American ginseng), a decrease in fasted blood glucose and HbA_{1c} has been reported in 24 type II diabetic patients following 8 weeks' administration of 1 g of a proprietary ginseng extract, taken 40 min before each meal (Vuksan *et al.*, 2000b). Of particular relevance to the present study, acute hypoglycaemic effects of *P. quinquefolius* have also been demonstrated in a series of randomized, placebo-controlled studies. Reductions in blood glucose levels, following a 25 g glucose challenge, have been reported during a 120 min oral glucose tolerance test in both diabetic patients who had ingested 3 g, 6 g and 9 g (Vuksan *et al.*, 2000a, c), and healthy participants administered 1 g, 2 g and 3 g of *P. quinquefolius* (Vuksan *et al.*, 2000a, 2001a). To date, the hypoglycaemic effects of single doses of *P. quinquefolius* or *P. ginseng* have not been assessed in the absence of a concomitant glucose load.

It has 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 (e.g. Foster *et al.*, 1998; Benton, 1990; Martin and Benton, 1999; Donohoe and Benton, 2000; Kennedy and Scholey, 2000; Scholey *et al.*, 2001; Sünram-Lea *et al.*, 2002a, b). 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. For example, a 25 g glucose drink improved performance on a more difficult (but not on an easier) mental arithmetic task, and the rate at which blood glucose fell correlated with performance on the same task (Kennedy and Scholey, 2000). Additionally, compared with placebo, a glucose drink improved performance during intense mental processing, which, in turn, led to a measurable reduction in blood glucose levels (Scholey *et al.*, 2001). One explanation for such findings is that increased uptake of blood glucose results in better performance. 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).

It seems likely that single doses of *P. ginseng*, in common with *P. quinquefolius*, may modulate blood glucose levels in healthy humans, and in particular may have hypoglycaemic properties related to modulation of glucose transport. In particular it is possible that ginseng administration may drive cellular glucose uptake which, at least acutely, may be available for metabolism during periods of effortful processing and thus improve performance. Given that cognitively demanding tasks may be the most sensitive to such effects, the present placebo-controlled, double-blind, balanced-crossover study investigated the effects of two separate single doses of *P. ginseng* (200 mg and 400 mg G115) on changes in fasted blood glucose levels and performance during sustained 'mentally demanding' tasks.

Subjects and methods

Participants

Sixteen female and 14 male undergraduate volunteers (mean age 22.6 years, S.D. 5.46) 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 30 participants, three were light smokers, and they agreed to abstain from smoking on the days of testing. All participants were overnight fasted, were alcohol-free for 12 h prior to baseline measure, and abstained from products containing caffeine on the days of testing. Volunteers were paid £60 for participation. Participants were randomly allocated a position on a Latin

Square counterbalancing the treatment order by the computerized generation of random numbers.

Blood glucose measurement

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

On each of the three active study days, blood glucose levels were measured via capillary finger prick at baseline, 1 h post treatment (before commencement of the first post-dose battery completion), and after the third (i.e. mid-point of testing) and sixth (i.e. end of testing) completions of the demand battery (see Fig. 1).

Cognitive demand battery

A 10 min, computerized 'cognitive demand battery' was utilized comprising the Serial Threes subtraction task (2 min), Serial Sevens subtraction task (2 min), a Rapid Visual Information Processing task (RVIP – 5 min), and a 'mental fatigue' visual analogue scale. 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). 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, 2001; Scholey *et al.*, 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), here using tests of 2 min 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 linear number pad 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 subtraction 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.

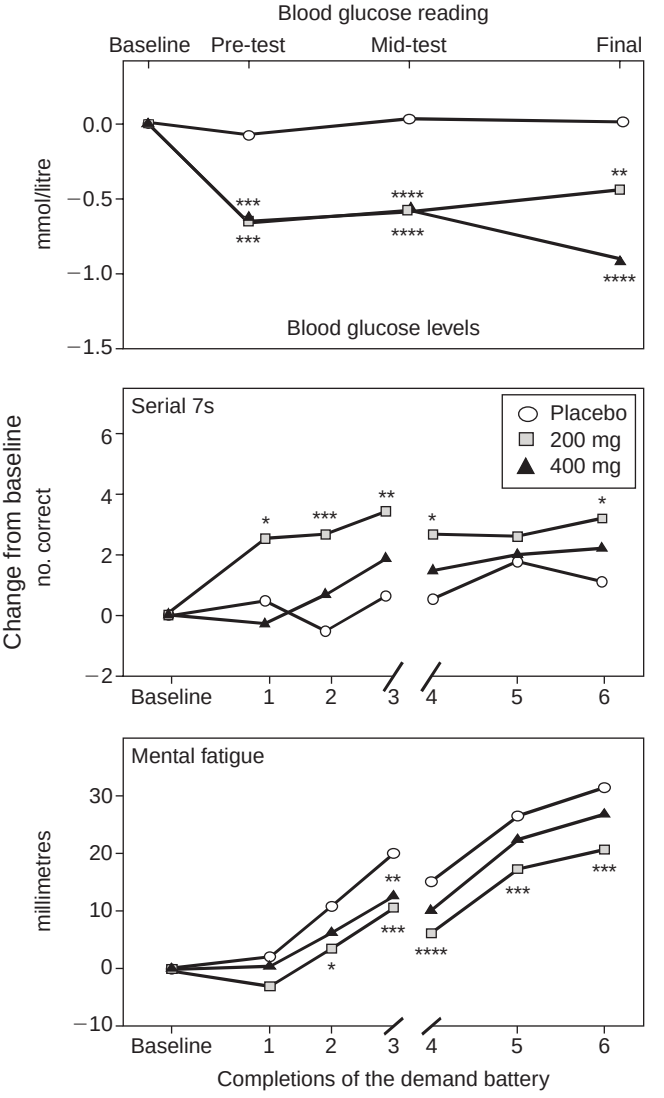

Figure 1 Effects of ginseng on blood glucose levels (top) Serial Subtractions (middle) and subjective ratings of mental fatigue (bottom). Top graph depicts mean change from baseline glucose level at 1 h post treatment (pre-test) and after three (mid-test) and six (final) post-dose completions of the battery. Middle and bottom graphs depict mean change from baseline scores at each post-dose completion (1 to 6) of the battery, for the Serial 7s subtraction task and for participants' subjective ratings of mental fatigue (lower scores indicate reduced mental fatigue). (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.005$; ****, $p < 0.001$; *****, $p < 0.0005$)

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 min 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 min, 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

Active treatments and placebo capsules, matched for size, colour, opacity and odour were provided by the manufacturer. Prior to the commencement of the study, a disinterested third party, who had no other involvement in the study, prepared the three 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.

On each study day, participants received four capsules. The individual capsules contained either an inert placebo, or 100 mg of *P. ginseng* extract (G115, Pharmaton SA, Lugano, Switzerland). Depending on the condition to which the participant was allocated on that particular day, the combination of capsules corresponded to a dose of 0 mg (placebo), 200 mg, or 400 mg of G115.

Procedure

Each participant was required to attend a practice day and three 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 regime according to a Latin Square that counterbalanced the order of treatments across the three active days of the study.

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

On the three remaining study days, after an initial practice run through the 10 min 'cognitive demand battery' (Serial Threes – 2 min, Serial Sevens – 2 min, RVIP – 5 min, Mental fatigue rating scale) on arriving at the laboratory (data not analysed), each participant completed the baseline 10-min cognitive demand battery pre-dose, followed immediately by ingestion of the treatment. Commencing 60 min after consuming the day's treatment the participants completed the demand battery six times in succession (i.e. a total of 60 minutes' task performance). Participants' blood glucose levels were measured pre-dose, 1 h post-dose (i.e. before commencing the cognitive tasks), after three completions (i.e. the mid-point of the post-dose tasks) and after the six completions of the 'cognitive demand battery' (see Fig. 1).

Statistics

Planned comparisons '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 (participant × treatment × demand battery completion), *a priori* planned comparisons were made between placebo and each of the active treatments (200 mg and 400 mg G115) at each time point utilizing *t* tests with MSError as an error term (Keppel, 1991). To ensure the overall protection level against Type I errors, comparisons were strictly planned prior to commencement of the study, only probabilities associated with planned comparisons were calculated, all planned comparisons were two-tailed, and the reporting and interpretation of results was restricted to measures that showed a pattern of results commensurate with a genuine treatment effect (i.e. in the event that a measure generated only a single significant planned comparison for a specific dose, the comparison was not interpreted).

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, mid-test and final were correlated with 'change from baseline' task performance at the nearest post-dose completion of the demand battery (i.e. the first, fourth and sixth completions). Correlations were conducted separately for each condition.

Results

Baseline scores

Prior to analysis of change from baseline data, raw baseline scores for all three conditions (placebo, 200 mg, 400 mg) 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. There were no significant differences in baseline performance on any measure. 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 represented in Table 1 and Table 2 respectively.

Blood glucose levels

Planned comparison revealed that, relative to placebo, there were significant reductions in blood glucose levels for both active treatments at all post-dose time points. As shown in Fig. 1a, 200 mg led to reductions at 1-h post-dose [$t(116) = 3.31$, $p = 0.001$], and

Table 1 Effects of Ginseng (G115) on blood glucose levels. Mean baseline glucose level and mean change from baseline glucose level at 1 h post treatment (pre-test) and after three (mid-test) and six (final) post-dose completions of the battery, with standard errors in italics. Significance (planned comparisons) is indicated in bold type ([B], $p < 0.01$; [C], $p < 0.005$; [D], $p < 0.001$; [E], $p < 0.0005$)

		Post-dose change from baseline		
Pre-dose baseline level		Pre-test	Mid-test	Final
Blood glucose levels (mmol)				
Placebo	5.336 *0.211*	−0.076 *0.248*	0.034 *0.258*	0.013 *0.216*
200 mg	5.681 *0.159*	**−0.646**[C] *0.176*	**−0.594**[D] *0.198*	**−0.432**[B] *0.182*
400 mg	5.939 *0.196*	**−0.664**[C] *0.214*	**−0.580**[D] *0.212*	**−0.933**[E] *0.213*

Table 2 Effects of Ginseng (G115) on cognitive outcome measures. Mean baseline and mean change from baseline scores, at each completion (1 to 6), are presented, 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)							
Higher score = increased fatigue							
Placebo	33.03 *4.360*	2.033 *2.942*	10.833 *3.569*	20.067 *4.535*	15.133 *4.975*	26.533 *4.675*	31.433 *4.638*
200 mg	37.90 *3.540*	−3.033 *2.710*	**3.533**[A] *2.910*	**10.633**[C] *3.078*	**6.200**[D] *3.663*	**17.300**[C] *3.456*	**20.667**[C] *3.802*
400 mg	35.26 *3.812*	0.400 *2.776*	6.200 *3.215*	**12.600**[B] *3.717*	10.100 *4.036*	22.367 *4.566*	26.767 *5.012*
RVIP reaction time (sec)							
Placebo	0.522 *0.015*	−0.015 *0.011*	−0.001 *0.011*	−0.009 *0.012*	−0.013 *0.012*	0.003 *0.015*	−0.015 *0.011*
200 mg	0.521 *0.011*	0.001 *0.008*	0.003 *0.012*	−0.002 *0.011*	0.009 *0.013*	**0.032**[A] *0.019*	−0.001 *0.009*
400 mg	0.529 *0.013*	−0.014 *0.010*	0.001 *0.011*	−0.007 *0.010*	0.007 *0.014*	0.018 *0.013*	**0.026**[D] *0.019*
RVIP (accuracy)							
Placebo	19.80 *1.223*	1.067 *0.783*	−0.967 *0.726*	−1.933 *0.798*	−1.667 *1.043*	−2.600 *1.112*	−2.900 *0.789*
200 mg	19.60 *1.363*	1.100 *0.703*	−0.900 *0.746*	−0.567 *0.718*	−1.433 *0.702*	−1.600 *0.887*	**−0.700**[B] *0.819*
400 mg	19.67 *1.214*	0.200 *0.680*	0.100 *0.808*	−0.533 *0.702*	−1.367 *0.701*	**−0.433**[B] *1.027*	−1.700 *0.739*
Serial 3s (no. correct)							
Placebo	42.30 *2.585*	1.067 *0.978*	2.867 *0.926*	0.300 *2.123*	−0.433 *1.575*	3.000 *1.571*	3.467 *1.352*
200 mg	42.67 *3.010*	0.900 *1.186*	2.600 *1.857*	2.400 *1.477*	**3.400**[B] *1.331*	3.567 *1.399*	3.833 *1.662*
400 mg	41.27 *2.367*	1.933 *1.033*	1.000 *0.922*	1.167 *1.685*	−1.100 *1.799*	0.467 *1.478*	**−1.033**[C] *1.915*
Serial 3s (errors)							
Placebo	2.80 *0.632*	0.300 *0.458*	−0.600 *0.386*	0.700 *0.735*	0.467 *0.321*	−0.700 *0.422*	−0.300 *0.476*
200 mg	1.93 *0.437*	0.567 *0.467*	**0.433**[A] *0.475*	0.567 *0.401*	0.567 *0.507*	**1.133**[E] *0.609*	−0.133 *0.299*
400 mg	2.30 *0.681*	0.067 *0.453*	**0.533**[A] *0.415*	0.233 *0.465*	0.500 *0.462*	−0.033 *0.452*	0.367 *0.484*
Serial 7s (no. correct)							
Placebo	24.37 *1.564*	0.467 *0.625*	−0.533 *1.069*	0.633 *1.072*	0.533 *1.032*	1.767 *0.926*	1.100 *1.151*
200 mg	22.50 *1.676*	**2.533**[A] *0.948*	**2.667**[C] *0.936*	**3.433**[B] *1.067*	**2.667**[A] *0.996*	2.600 *1.202*	**3.200**[A] *1.261*
400 mg	22.57 *1.334*	−0.300 *1.042*	0.667 *0.930*	1.867 *0.942*	1.467 *1.145*	2.000 *1.055*	2.200 *1.159*
Serial 7's (errors)							
Placebo	1.73 *0.322*	0.167 *0.497*	0.767 *0.444*	0.633 *0.439*	0.533 *0.587*	0.733 *0.453*	1.000 *0.699*
200 mg	1.80 *0.341*	−0.100 *0.459*	0.567 *0.538*	0.733 *0.551*	1.367 *0.714*	0.367 *0.585*	0.800 *0.648*
400 mg	1.80 *0.430*	0.167 *0.363*	−0.033 *0.481*	0.467 *0.392*	0.733 *0.359*	0.333 *0.419*	0.500 *0.418*

after three [$t(116) = 3.65$, $p = 0.0003$] and six [$t(116) = 2.58$, $p = 0.01$] post-dose completions of the demand battery. The 400 mg treatment also led to reductions at 1-h post-dose [$t(116) = 3.42$, $p = 0.0007$], and after three [$t(116) = 3.57$, $p = 0.0004$] and six [$t(116) = 5.50$, $p = 0.0000001$] completions of the demand battery.

Serial Threes

There were no interpretable significant differences in performance of the Serial Threes subtraction task (Table 2).

Serial Sevens

A greater number of correct subtractions were made on the Serial Sevens task following 200 mg. Participants made more correct responses on the first [$t(290) = 2.056$, $p = 0.041$], second [$t(290) = 3.18$, $p = 0.002$], third [$t(290) = 2.78$, $p = 0.006$], fourth [$t(290) = 2.12$, $p = 0.035$], and sixth post-dose completions [$t(290) = 2.09$, $p = 0.038$] of the cognitive demand battery (Fig. 1b).

Rapid Visual Information Processing task (RVIP)

There were no interpretable significant differences in the performance of the RVIP task (Table 2).

Mental fatigue

An attenuation of the increase in subjective ratings of mental fatigue suffered as a consequence of extended task completion was revealed for both active treatments. 400 mg led to reductions in subjective ratings of mental fatigue during the third [$t(290) = 2.62$, $p = 0.009$] completion of the demand battery, whilst 200 mg led to reductions on the second [$t(290) = 2.56$, $p = 0.011$], third [$t(290) = 3.31$, $p = 0.001$], fourth [$t(290) = 3.14$, $p = 0.002$], fifth [$t(290) = 3.24$, $p = 0.001$], and sixth [$t(290) = 3.78$, $p = 0.0002$] completions of the demand battery (Fig. 1c).

Correlations

There were no significant correlations between the change in blood glucose levels evinced in any of the three conditions and 'change from baseline' task performance at the completion of the battery nearest to the blood glucose reading.

Discussion

The results of the present placebo-controlled study demonstrate that single doses of *P. ginseng* (G115) administered to healthy young volunteers can lower circulating blood glucose levels, enhance cognitive performance of a mentally demanding task (Serial Sevens), and ameliorate the increase in subjective feelings of mental fatigue experienced by participants during sustained intense cognitive processing.

Both 200 mg and 400 mg of *P. ginseng* (G115) led to significant reductions in circulating blood glucose levels at all three post-treatment time points measured. To our knowledge this is the first demonstration of *P. ginseng's* acute hypoglycaemia-inducing properties in healthy, overnight-fasted human volunteers. Research has previously addressed the chronic effects of both *P. ginseng* (Sotaniemi *et al.*, 1995; Vuksan *et al*, 2000a) and *P. quinquefolius* (Tetsutani *et al.*, 2000) and the acute effects of the latter on the glycaemic response to a glucose challenge (Vuksan *et al.*, 2000c, 2001a; Sievenpiper *et al.*, 2003a, b, 2004). The acute hypoglycaemic effect of *American ginseng*, following a 25 g glucose load, has been reported in both diabetic patients who had ingested 3 g, 6 g and 9 g *P. quinquefolius* (Vuksan *et al.*, 2000a, c), and non-diabetics administered 1 g, 2 g and 3 g (Vuksan *et al.*, 2000a, 2001a). This effect, however, was restricted to a batch of *P. quinquefolius* with a specific total ginsenosides content (3.54%) and protopanaxadiol: protopanaxatriol ratio (2:4) (Sievenpiper *et al.*, 2003a). Additionally Sievenpiper *et al.* (2004) reported that there was no effect of eight other widely-used *ginseng* types (*Sanchi, Siberian, American, Asian, Korean red, Japanese, wild American and Vietnamese*) on indices of glycaemic control following a 75 g oral glucose tolerance test. However, an extract of *P. ginseng* was associated with increased blood glucose levels and insulin response following the glucose load (Sievenpiper *et al.*, 2003). The effects of *P. ginseng* in the absence (as here) and presence of a glucose load may reflect the differential working of a single gluco-regulatory mechanism, and this possibility requires further investigation.

With regards cognitive performance, the only meaningful significant effects of *P. ginseng* were seen during performance of the most difficult task (Serial Sevens). The 200 mg dose of ginseng extract led to a significantly greater number of correct subtractions being carried out on all post-dose battery completions (with the exception of the fifth). This improved speed of performance was not associated with more errors, precluding the possibility of any treatment-specific 'speed/accuracy trade-off'. The improved performance following a 200 mg dose of *P. ginseng* is consistent with the recent findings of faster memory, attention and serial subtraction task performance (Kennedy *et al.*, 2004), and decreased latency of the P300 component of auditory evoked potentials following the same dose (Kennedy *et al.*, 2003). The accumulation of findings of positive effects on the speed of task performance does suggest that the original observation of slower attention (Kennedy *et al.*, 2001a) and Serial Sevens (Scholey and Kennedy, 2002) task performance may have been anomalous. The most parsimonious explanation for this is that of a simple cohort effect (both studies reported data from the same cohort). Alternatively, whilst the extract used is standardized to total ginsenoside content, it is possible that even minor differences in the levels of single ginsenosides, or groups of ginsenosides (e.g. the ratio of panaxadiols to panaxatriols), may have exerted an effect.

In relation to the reported subjective feelings of mental fatigue, it was found that the 200 mg treatment led to a significant amelioration in the participants' subjective feelings of mental fatigue at all post-dose time points (except the first post-dose battery completion). The 400 mg dose led to a significant reduction in ratings

of mental fatigue after the third battery completion only. This is the first reported human study that has examined the effect of *P. ginseng* on subjective feelings of mental fatigue associated with intense cognitive processing. A number of studies have, however, demonstrated that ginseng or its active components can attenuate the effects of fatigue in night nurses (Wesnes *et al.*, 2003), and improve measures pertaining to 'quality of life' or 'well being' in pathological (Neri *et al.*, 1995; Sotaniemi *et al.*, 1995; Tode *et al.*, 1999) and healthy (Wiklund *et al.*, 1994; Marasco *et al.*, 1996; Ellis and Reddy, 2002) human populations (although findings of this nature are by no means unequivocal (Kennedy and Scholey, 2003)). The relationship between acute and chronic effects merits further investigation.

Since both improvements in performance and amelioration of mental fatigue were associated with the same 200 mg dose, it is possible that the effects on either measure were secondary to those on the other. Unfortunately, the current study was not designed to address this potential cause-and-effect issue. Similarly, studies of ginseng's acute effects have not directly measured performance-related fatigue (although they have included measures of mood), and it is possible that the previously demonstrated cognitive effects are as a consequence of altered fatigue levels.

The mechanisms responsible either for ginseng's hypoglycaemic 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 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 from a number of studies. For example, there is evidence of enhanced NO synthesis by total ginsenosides (Chen and Lee, 1995; Chen *et al.*, 1997), the PPT fraction (Kim *et al.*, 1992), and single ginsenosides such as Rg_1 (Kim *et al.*, 1992; Kang *et al.*, 1995), Re (Kim *et al.*, 1992), Rg_3 (Kim *et al.*, 1998) and Rc (Kim *et al.*, 1998). These effects have been seen in nervous tissue (Kim *et al.*, 1998; Vuksan and Sievenpiper, 2000), kidney (Han and Kim, 1996) and aorta (Kang *et al.*, 1995). Increased plasma NO concentrations have also been demonstrated following 8 weeks' administrating of *American ginseng* in type 2 diabetics (Xu *et al.*, 2000). This increase in NO correlated with improvements observed in HbA_{1c}. Certain ginsenosides have also shown effects consistent with cholinergic stimulation (Salim *et al.*, 1997; Yamaguchi *et al.*, 1997), and adrenergic blockade (Kudo *et al.*, 1998; Tachikawa *et al.*, 1999), with such changes in either system potentially resulting in increased glucose uptake (Xie and Lautt, 1996; Lekas *et al.*, 1999). The Asian ginseng extract G115 has also been shown to increase 2-Deoxy-D-[2-^{3}H]glucose (2-DG) uptake in a dose-dependent manner (Samira *et al.*, 1985). Opposing glycaemic effects of ginseng and specific ginsenosides have also been documented. Hong *et al.* (2000) showed that a water extract of Asian ginseng significantly inhibited insulin stimulated 2-DG uptake, whereas Kimura *et al.* (1981) showed that an extract containing Rb and Rc increased glycaemia at 100 mg/kg. It is possible that in the current study ginseng improved performance by modulating some aspect of the mechanisms responsible for the reciprocal relationship between falling blood glucose and improved performance during cognitive demand. One (highly speculative) possibility is that *P. ginseng* promotes the transport of glucose (including into active cells) and thus facilitates metabolism in task-sensitive structures. This is consistent with the findings reported here, showing a combination of reduced blood glucose, improved performance and reduced mental fatigue. Further studies are needed to elucidate any such processes, including examining the cognitive effects of co-administration of glucose with ginseng.

Whatever the outcome of such studies, it is clear that ginseng's ability to modulate human cognitive performance could be attributable to a single effect, or a combination of effects, on a wide number of physiological parameters. One conclusion that might be drawn from the current results, given the lack of any correlational relationship between the modulation of glucose level and cognitive performance, is that the mechanism underlying the improved performance on the most difficult task seen here is unlikely to be a direct modulation of blood glucose levels. Indeed, whilst little research has directly addressed the correlation between cognitive effects and the manipulation of blood glucose levels, previous research would suggest that reduced blood glucose levels, as here, would have led to a decline in task performance (e.g. Holmes *et al.*, 1984; Gold *et al.*, 1985; De Feo *et al.*, 1988; Taylor and Rachman, 1988; Sünram-Lea *et al*., 2001; Scholey *et al.*, 2005b). The possibility remains that both effects are as a consequence of improved utilization and metabolism of circulating glucose, but it seems equally likely, in the absence of a cognitive effect for 400 mg, that they reflect differing mechanisms. Whilst the lack of a cognitive effect following 400 mg may appear curious, previous ginseng research, both in humans and animals, is replete with dose-specific effects and non-linear dose response profiles (for review, see Kennedy and Scholey, 2003).

The importance of the observed hypoglycaemic effect in the present study should not be understated. Diabetes Mellitus, and the treatment of diabetes, remains a major and growing health problem. Vuksan *et al.* (2001b) have provided evidence to suggest that *P. quinquefolius* (American ginseng) may be an effective alternative therapy for patients suffering from type 2 diabetes. The present findings suggest that *P. ginseng* (G115) may have a similar therapeutic value. Additionally, the cognitive deficits in a number of conditions may be related in part to poor gluco-regulation, for example, ageing (Hall *et al.*, 1989), Alzheimer's disease (Hoyer, 2000) and schizophrenia (Schultz, 1999). It is possible that ginseng may have a positive (or negative) effect on this aspect of such disorders. However, until further research has delineated the mechanisms underlying the demonstrated gluco-regulatory effects, caution should be exercised in the use of this product by sufferers from diabetes.

In conclusion, both doses of *P. ginseng* utilized here led to reduced levels of circulating blood glucose. The lower (200 mg) dose also 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 possibility that members of the Panax genus may eventually provide a natural, well-tolerated treatment

for diabetes (Vuksan *et al.*, 2001b) the mechanisms underlying these effects require further investigation.

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