Nutrition Research Reviews (2005), **18**, 77–88
DOI: 10.1079/NRR2005103

The role of functional foods in the psychobiology of health and disease

Mark Hamer[1]*, Gail Owen[2] and Joris Kloek[2]

[1]*Psychobiology Group, Department of Epidemiology and Public Health, University College London, 1–19 Torrington Place, London WC1E 6BT, UK*
[2]*Unilever Health Institute, Unilever R&D Vlaardingen, The Netherlands*

The effect of psychological stress on health is becoming a serious concern, with figures from the World Health Organization showing that stress-related disorders affect nearly 450 million individuals worldwide. Heightened physiological stress responses and psychosocial factors have been linked to disease pathways such as hypertension and CVD. This has prompted significant interest within the scientific community, public health bodies and industry to employ interventions to control and reduce the impact of stress on health. There is now strong potential for functional foods to offer stress management benefits. Various physiological pathways have been targeted by specific dietary supplements for stress reduction, including the hypothalamic–pituitary–adrenal axis and sympathetic nervous system. Presently there are a number of ingredients, which include vitamin C, milk proteins, a number of herbal extracts (ginkgo biloba, ginseng, kava, valerian and lemon balm), and *n*-3 fatty acids, that have demonstrated potential stress reactivity-lowering and mood-enhancing effects, although further work is required to substantiate the efficacy in human subjects. Dietary supplements that can alleviate excessive stress responses may play an increasingly important role for the maintenance of health in a stressful environment. However, future research should employ a greater range of measures that will provide stronger evidence to substantiate functional food claims for stress relief.

Psychosocial stress: Cardiovascular disease: Stress relief: Anxiety: Bioactive compounds

Introduction

The psychobiology of health and disease can be broadly defined as the influence of psychosocial stress on biological mechanisms that influence disease pathways. Stress is common in most people's lives and although a certain degree of stress is beneficial to stimulate mental and physical performance, the inability to cope with excessive stress responses may be detrimental. Figures from the World Health Organization show that stress-related disorders affect nearly 450 million individuals worldwide (World Health Organization, 2001). US health authorities estimate that 19 million Americans suffer from anxiety disorders (National Institute of Mental Health, 1994) and half a million individuals in Great Britain believe that work-related stress is making them ill (Health and Safety Executive, 2002). Emerging and existing scientific evidence has demonstrated that heightened blood pressure (BP) responses to psychosocial stress are predictors of hypertension (Carroll *et al.* 2003; Matthews *et al.* 2004) and progression of carotid atherosclerosis (Barnett *et al.* 1997; Kamarck *et al.* 1997; Jennings *et al.* 2004). For example, recent data from the Coronary Artery Risk Development in Young Adults (CARDIA) study showed that among 4100 black and white American adults exposed to three psychological stress tasks (cold pressor, star tracing, and video game), those subjects displaying higher BP responses to the tasks demonstrated significantly earlier occurrence of hypertension during 13 years of follow-up, after controlling for traditional hypertension risk factors (Matthews *et al.* 2004). Further recent data from a sample of 756 men showed that BP reactions to mental stress were strongly related to the progression of carotid intima-media thickness (IMT) and mean IMT after a 7-year follow-up despite adjustment for standard risk factors (Jennings *et al.* 2004). Similarly, there is strong evidence to support a causal relationship between chronic stress, depression, and social support and the development of coronary artery disease (Rozanski *et al.* 1999; Strike & Steptoe, 2004). Therefore it is important to examine and implement healthcare interventions that control the impact of stress on health.

Abbreviations: BP, blood pressure; DHA, docosahexaenoic acid; HPA, hypothalamic–pituitary–adrenal; HR, heart rate; IMT, intima-media thickness; LNAA, large neutral amino acid; PBR, peripheral-type benzodiazepine receptor; Trp, tryptophan.

* **Corresponding author:** Dr Mark Hamer, fax +44 20 7916 8542, email m.hamer@ucl.ac.uk

Previous research has demonstrated the link between nutrient intake and stress (Epel *et al.* 2001; Wardle & Gibson, 2002; Dallman *et al.* 2003). For example, Dallman *et al.* (2003) proposed that individuals eat comfort food (sweet, fatty foods) in an attempt to reduce excessive stress-induced responses. Furthermore, female participants who were high cortisol reactors to a psychosocial stress task consumed more energy on the stress day compared with low reactors (Epel *et al.* 2001). Healthy eating has recently been included in the current recommendations for coping with stress (British Heart Foundation, 2004) because it is now recognised that dietary intake can have a beneficial impact on health beyond the basic provision of energy and essential nutrients. Thus, there is considerable potential for functional foods to offer stress-coping benefits. Functional foods can be defined as 'foods and beverages with claimed health benefits based on scientific evidence' (Diplock *et al.* 1999). As such, functional food bridges the gap between ordinary foods, aimed to maintain adequate nutritional status, and pharmaceutical agents, drugs aimed to diagnose, prevent, cure or treat an illness. The basis of functional foods is bioactive compounds that may be incorporated into an existing food or liquid matrix or may be consumed in the more traditional form of a dietary supplement. However, the opportunity to provide foods and supplements to consumers for stress relief and mood enhancement has resulted in products that have little scientific underpinning, with claims that remain dubious. Therefore, the purpose of the present review is to critically examine foods and dietary supplements that are claimed to provide stress relief.

Psychobiological targets for lowering the stress response

There are two important aspects of the physiological stress response that have been targeted by dietary supplements. These include the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system. A variety of psychological tasks (for example, mental arithmetic, Stroop word-colour, speech role-play) can be employed to experimentally elicit a stress response in the laboratory. Factors such as genetic characteristics, age, sex, body composition, blood lipids, personality characteristics, and appraisals appear to contribute to the size and pattern of the response. The stress response is largely driven by cortisol (released by the HPA axis) and the catecholamines (released by the sympathetic nervous system) that produce a number of physiological responses in the cardiovascular and immune systems. Common physiological responses to an acute laboratory stress task include increased BP, heart rate (HR), and cardiac output, skeletal muscle vasodilatation, endothelial dysfunction, renal vasoconstriction, insulin resistance, blood platelet activation, release of inflammatory markers, and immune cell activation (Weiner, 1992; Hugdahl, 1996). A number of psychobiological measures and techniques can be employed to assess the stress response (summarised in Table 1).

The mechanisms associated with chronic stress-induced disease pathways are closely linked with the physiological responses to acute stressors. For example, a direct effect of an exaggerated BP response is an increased biomechanical stimulus in the endothelium caused by pulsatile blood flow and changes in the shear forces imposed by blood flow under increased pressure. At specific sites that are most exposed to changes in blood flow (increased turbulence and changes in shear stress) researchers have found atheromatous plaques in primate models of chronic stress (Kaplan *et al.* 1991; Manuck *et al.* 2000) and in human atherosclerotic disease (Black & Garbutt, 2002). Endothelial dysfunction plays a key role in the initiation of atherosclerosis because NO production from healthy endothelial cells has an anti-atherogenic effect by inhibiting cellular adhesion, migration, and proliferation responses (Lüscher & Vanhoutte, 1990; Ross, 1999). Other stress-induced disease pathways appear to be linked with changes in sympathovagal balance (Singh *et al.* 1998; Vrijkotte *et al.* 2000), inflammation (Black & Garbutt, 2002; Black, 2003), vascular remodelling processes (Folkow, 1990), and specific cortisol response profiles (Sapolsky *et al.* 1986, 1991; Sapolsky, 1990, 1996).

Psychological targets for lowering the stress response

As well as driving the physiological response, hormones that are sensitive to stressful or arousing situations also regulate important psychological variables. Cortisol, for example, is a major counter-regulatory hormone involved in

Table 1. An overview of the types of measures and techniques employed in psychobiological studies

Techniques	Variables measured	Available overviews
Impedance cardiography and electrocardiogram	HR, CO, SV, TPR, cardiac contractility	Miles & Gotshall (1989); Sherwood *et al.* (1990)
Ausculatory method, Finapres, and automated oscillometric devices	BP, ambulatory BP	O'Brien *et al.* (2003); Parati *et al.* (2004)
Venous occlusion plethysmography and vascular ultrasound	BF, VR, endothelial function	Radegran (1999); Faulx *et al.* (2003)
Microneurography and spectral analysis	Sympathetic outflow, sympathovagal balance	Grassi & Esler (1999)
ELISA, RIA	Cortisol, catecholamines, immune and inflammatory markers, haemostatic factors	Goldstein & McDonald (1986)
Common psychometric tools: PSS, STAI, POMS, CSI	Perceived stress, anxiety, mood, coping	Speilberger (1983); Cohen & Williamson (1988); Carver *et al.* (1989); Little & Penman (1989)

HR, heart rate; CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance; BP, blood pressure; BF, blood flow; VR, vascular resistance; PSS, perceived stress scale; STAI, state-trait anxiety inventory; POMS, profile of mood states; CSI, coping style inventory.

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glucose homeostasis. Glucose is the primary source of energy for brain function and cortisol can inhibit hippocampal glucose uptake (Horner *et al.* 1990) or metabolism (de Leon *et al.* 1997). A number of studies have shown that cortisol impairs mental performance in relation to food intake (Gibson & Green, 2002), and particularly those functions associated with hippocampal function such as memory (for example, Kirschbaum *et al.* 1996; Lupien *et al.* 1999). Individual differences in vulnerability to stress may therefore be measured by differences in cognitive performance during psychologically challenging situations, such as cognitive performance testing.

In addition to cognition, subjective mood can provide a useful means to measure stress. There is a strong connection between mood state and psychobiological responses; that is, negative mood states such as depression and anxiety have been associated with elevations in BP during ambulatory monitoring (Schwartz *et al.* 1994), higher cortisol output over the day (van Eck *et al.* 1996), and elevated levels of circulating pro-inflammatory cytokines (Strike *et al.* 2004).

Nutrients for stress relief

A number of studies in human subjects (see Table 2) and animals have examined the efficacy of nutritional intervention for lowering the biological response to stress in relation to the HPA axis and sympathetic nervous system. In addition, some of these studies have reported improvements in psychological outcomes such as cognitive performance, mood and anxiety, although the aim of the present review is not to provide an in-depth review of the effects of nutrients on mood. Thus, the review focuses on psychobiological studies in human subjects and will summarise key studies in animals.

Carbohydrate, proteins and tryptophan

Markus *et al.* (2000*a*,*b*) have performed dietary intervention studies that were designed to increase the plasma tryptophan (Trp):large neutral amino acid (LNAA) ratio, thereby enhancing brain serotonergic activity that has been hypothesised to improve the ability to cope with stress. In the first study plasma Trp:LNAA was increased by 42 % in subjects that were administered two high-carbohydrate (66 %) low-protein (3·6 %) meals compared with high-protein (27 %) low-carbohydrate (41 %) meals (Markus *et al.* 2000*b*). The administration of the high-carbohydrate meals significantly reduced the cortisol response to a laboratory stress task in subjects highly prone to stress, although the HR response was unaffected by the intervention (BP not measured). In contrast, Gonzalez-Bono *et al.* (2002) reported that glucose, but not protein or fat load, administered 1 h before a stress task amplified the cortisol response in healthy subjects. Similarly, Kirschbaum *et al.* (1997) demonstrated that a glucose load before a stressful task provokes a greater cortisol response to the stress, with post-load plasma glucose level predicting the extent of the rise in cortisol. These inconsistencies may be largely explained by differences in the nutritional feeding strategy. That is, Markus *et al.* (2000*b*) administered breakfast and lunch before stress testing, whereas other researchers such as Gonzalez-Bono *et al.* (2002) administered one liquid meal after an 8 h fast before the stress test, both of which were performed in the afternoon. The effects might also be specific to glucose loads rather than other macronutrients. That glucose, but not fat or protein, affected the HPA axis response to stress in the later study suggests the involvement of a central mechanism related to glucose-mediated HPA regulation. Choi *et al.* (1996) have proposed that high glucose and insulin levels stimulate activity of the ventromedial nuclei, which in turn stimulates the paraventricular nuclei resulting in HPA axis activation. Given that activation of the HPA axis is associated with increased cortisol secretion, this might also help to explain why meals that produce large increases in plasma glucose result in memory impairment relative to meals with a lower glycaemic index (Benton *et al.* 2003). Furthermore, glucose intolerance is associated with increased awakening cortisol levels (Reynolds *et al.* 2001), elevated cortisol secretion after stress (Rosmond & Björntorp, 2000), and abnormal metabolism of, and increased tissue sensitivity to cortisol (Andrews *et al.* 2002). These data corroborate the hypothesis that excessive cortisol secretion is related to the development of abdominal obesity (Rosmond *et al.* 1998).

In a double-blind placebo-controlled trial, Markus *et al.* (2000*a*) administered a dietary milk protein enriched in Trp (α-lactalbumin) that had a similar effect of increasing plasma Trp:LNAA by 48 %. In the most stress-sensitive individuals there was also a reduction in the cortisol response and depressive mood following exposure to a laboratory stressor. However, these results were confounded by a greater baseline cortisol level in the experimental compared with placebo condition. A further study using α-lactalbumin that produced a 43 % increase in plasma Trp:LNAA showed a significant interaction between diet and stress vulnerability on a test of memory function, indicating that dietary Trp increases cognitive performance in individuals vulnerable to stress (Markus *et al.* 2002). The serotonin–stress link appears to be highly complex. Increases in brain serotonin appear to modulate adrenocortical reactivity probably through alterations in 5-HT1a and 5-HT2 receptor sites located at the hypothalamic and pituitary brain area (Maes & Meltzer, 1995). The different serotonergic pathways appear to initiate as well as terminate the adrenocorticol axis (Graeff *et al.* 1996); this possibly explains why baseline cortisol level was elevated during the α-lactalbumin intervention period described above.

Another aspect of the carbohydrate–stress interaction relates to the action of insulin on the adrenergic nervous system. Jern (1991) conducted a randomised, placebo-controlled, and double-blind study in healthy subjects to study the effects of acute carbohydrate administration on central and peripheral cardiovascular responses to a 15 min mental arithmetic task. Oral glucose administration (1 g/kg body weight) induced hyperinsulinaemia that was characterised by a significantly increased systemic vascular resistance response to the stress task, in comparison with the placebo group, which demonstrated increases in cardiac output but not resistance. Those exaggerated systemic vascular resistance responses to stress have been seen in

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Table 2. Key studies examining the effects of nutrients on psychobiological responses in human subjects

Ingredient and study	Intervention and design	Subjects	Evidence of nutrient uptake and compliance	Type of stressor	Results
Carbohydrate					
Markus *et al.* (2000*b*)	Acute study: randomised design with subjects acting as their own control. High-CHO low-protein meal (66 %, 4 %) or low-CHO high-protein meals (41 %, 27 %) on separate days (given 1·5 h pre-stress)	High stress (*n* 22) and low stress (*n* 23) healthy M and F (19–26 years)	↑ Plasma Trp:LNAA ratio in high CHO group	Mental arithmetic under noise (18 min) on each day	↓ Cortisol response and ↓ feelings of depression in high stress subjects on high-CHO diet. No effect on HR response
Gonzalez-Bono *et al.* (2002)	Acute study: randomised, parallel, controlled. Four groups: glucose (75 g); protein (83 g); fat (80 g); water (control) (given 1 h pre-stressor)	Healthy M (*n* 37) (23 ± 0·4 years)	Blood glucose	Trier Social Stress Test (10 min)	↑ Cortisol response in glucose group. No differences in mood and perceived stress. Cortisol response and blood glucose changes positively correlated (r 0·49; $P < 0·05$)
Jern (1991)	Acute study: randomised, placebo-controlled, double-blind with subjects acting as their own control. Glucose drink (1 g/kg BW) or placebo 1 week apart (given 70 min pre-stress)	Healthy M (*n* 10) (24–36 years)	Blood glucose and insulin	Mental arithmetic (15 min)	Similar BP response to stress although pattern of response differed: glucose feeding induced ↑ PVR compared with an ↑ CO in placebo
α-Lactalbumin					
Markus *et al.* (2000*a*)	Acute study: double-blind, placebo-controlled. α-Lactalbumin diet (Trp:LNAA ratio 8·7) or casein diet (Trp:LNAA ratio 4·7) on separate days (given 1·5 h pre-stressor)	High stress (*n* 29) and low stress (*n* 29) healthy M and F (17–34 years)	↑ Plasma Trp:LNAA ratio in α-lactalbumin subjects	Mental arithmetic under noise (18 min) on each day	↓ Cortisol response and ↓ feelings of depression in high stress subjects on α-lactalbumin diet
Ginkgo biloba					
Jezova *et al.* (2002)	Acute study: parallel, randomised, double-blind, placebo-controlled. Single 120 mg dose ginkgo biloba (EGb 761) (given 30 min pre-stressor)	Healthy M and F (*n* 70) (20–30 years)	None	Memory test (6 min), 2 × 3 min static handgrip exercise (30 % MVC)	↓ SBP and DBP response to stressor in EGb 761 group. Prevention of cortisol rise in males from EGb 761 group. No effect on HR
Ginseng					
Facchinetti *et al.* (2002)	Chronic: parallel, randomised, double-blind, placebo-controlled. Two vials *Eleutherococcus senticosus*/d for 30 d	Healthy M and F (*n* 45) (18–30 years)	None	Stroop task (3 × 45 s) before and after intervention	↓ SBP and ↓ HR response in placebo and ginseng groups. No significant difference in effects
Valerian and kava					
Cropley *et al.* (2002)	Chronic: parallel, randomised, non-placebo-controlled. Three groups: valerian (600 mg/d for 7 d); kava (120 mg/d for 7 d); non-placebo control	Healthy M and F (*n* 54) (18–30 years)	None	Stoop task (6 min) before and after intervention	↓ SBP response in kava and valerian groups, no effect in control. ↓ HR response in valerian group only; ↓ perceived task pressure for both groups
Vitamin C					
Brody *et al.* (2002)	Chronic: parallel, randomised, double-blind, placebo-controlled. Vitamin C (3 g/d for 14 d)	Healthy M and F (*n* 120) (19–40 years)	↑ Plasma vitamin C level. Diaries and unused capsules collected	Trier Social Stress Test (10 min). Administered once after intervention	↓ SBP response, ↓ perceived stress, greater cortisol recovery in vitamin C group

Table 2. *Continued*

Ingredient and study	Intervention and design	Subjects	Evidence of nutrient uptake and compliance	Type of stressor	Results
Micronutrient mix Taylor *et al.* (2003)	Chronic: parallel, placebo-controlled. Vitamin and trace element supplement for 12 weeks	Healthy students (*n* 22)	None	Examination stress	No effects on cytokines (IL-6, TNF-α) or anxiety, depression, perceived stress
n-3 and *n*-6 Sawazaki *et al.* (1999)	Chronic: parallel, randomised, double-blind, placebo-controlled 1·5 g DHA/d for 9 weeks	Healthy M and F (*n* 14) (21–25 years)	↑ Erythrocyte EPA and DHA content	Twenty stressful medical exams (9-week period). Stress levels were confirmed by interview	↓ NA in DHA group after examination period; ↓ cortisol in placebo but not DHA group after examinations. Adrenaline levels unaffected.
Delarue *et al.* (2003)	Chronic: 1·1 g EPA/d + 0·7 g DHA/d for 3 weeks (no control)	Healthy M (*n* 7) (23 ± 1·3 years)	None	Mental arithmetic and Stroop task (30 min) before and after intervention	Cortisol response abolished, adrenaline response blunted, NA response unaffected
Deferne & Leeds (1996)	Chronic: parallel, randomised, placebo-controlled. γ-Linolenic acid or safflower-seed-oil placebo (6 g/d for 8 weeks)	Borderline hypertensive M (*n* 27) (42 years)	↑ Plasma *n*-6 profile. Food diaries and unused capsules collected	5 min mental arithmetic before and after intervention	↓ BP response to stress task in γ-linolenic acid group

CHO, carbohydrate; M, male; F, female; Trp, tryptophan; LNAA, large neutral amino acid; HR, heart rate; BW, body weight; BP, blood pressure; PVR, peripheral vascular resistance; CO, cardiac output; SBP, systolic blood pressure; DBP, diastolic blood pressure; MVC, maximum voluntary contraction; DHA, docosahexaenoic acid; NA, noradrenaline.

central obesity and related to a risk factor for hypertension development (Jern *et al.* 1992), which suggests that ingestion of high-glycaemic carbohydrates may have unfavourable effects on the cardiovascular system, despite being potentially beneficial for enhancing brain serotonergic activity.

Herbal extracts

Jezova *et al.* (2002) performed a parallel, randomised, double-blind, placebo-controlled trial in seventy healthy subjects (thirty-three male, thirty-seven female) to examine the effect of a single dose (120 mg) of ginkgo biloba on BP and cortisol responses to a combined mental and physical stressor. The stressor consisted of a memory test followed immediately by two 3 min bouts of static handgrip exercise at 30 % of maximum voluntary contraction. The experimental group demonstrated a significant reduction in systolic BP and diastolic BP response (of approximately 10 mmHg), but not HR, during the combined stressor, and cortisol was significantly reduced post-stress only in males. That the BP response was comparatively large (30 mmHg increase in control group) compared with a standard response for a mental challenge alone suggests that the handgrip exercise was predominantly responsible for this response. Therefore, the data are difficult to interpret given that the mechanisms for BP responses to isometric exercise are different compared with the response to mental challenge alone. Nevertheless, these are the only data in human subjects to demonstrate an effect of ginkgo biloba on the BP and cortisol responses to stress. The mechanisms are thought to be associated with modulation of the adrenal cortical peripheral-type benzodiazepine receptor (PBR) and/or inhibition of glutamate receptors (Amri *et al.* 1997, 2003).

Numerous studies have examined the efficacy of ginkgo biloba for improving mood and cognition. A review of studies relating to 'cerebral insufficiency', which is characterised by anxiety, depression and tiredness, as well as confusion and memory impairment, showed that ginkgo biloba produced clinically significant improvements in symptoms after a minimum of 6 weeks of treatment (Kleijnen & Knipschild, 1992). Doses ranged between 120 and 160 mg/d.

The Stroop task, which is an incongruent task that consists of identifying colours from colour words in contrasting colours of ink, has been used to demonstrate the efficacy of herbal interventions for lowering cardiovascular responses to stress. For example, Facchinetti *et al.* (2002) examined the effect of supplementation with ginseng root extract (*Eleutherococcus senticosus*; unspecified dose taken for 30 d) in a randomised placebo-controlled trial. The authors claimed that treatment with the ginseng extract significantly reduced BP and HR responses to the Stroop task, although closer inspection of the data shows that marked reductions in reactivity to the post-treatment Stroop task are also evident in the placebo group. Thus, this would suggest reductions in reactivity were due to habituation to the task and not due to the ginseng intervention. The data reported in studies of subjective mood are equally equivocal for ginseng. Although a recent review (Coleman *et al.* 2003)

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found that various components relating to overall health and quality of life are improved with ginseng, it is difficult to attribute an overall change in psychological state to ginseng. Similarly, standardised mood questionnaires often fail to show any positive outcome of ginseng on affective state (Cardinal & Engels, 2001), although a combined ginseng and ginkgo biloba (600 and 360 mg respectively) improved self-reported contentment in young, healthy subjects (Kennedy *et al.* 2002*b*).

The Stroop mental stress task has been used to test the efficacy of other herbal ingredients. Cropley *et al.* (2002) administered a standard dose of kava (*n* 18) or valerian (*n* 18) for 7 d and observed significant reductions in the systolic BP response to the stress task (−4 mmHg) in comparison with the baseline stress response, whilst the control group (*n* 18) remained unchanged. Further reductions in HR reactivity (−4 beats/min) were observed for the valerian group. The participants from the kava and valerian groups also experienced a significant reduction in the psychological pressure that they felt they were under during the Stroop task, which was measured using a seven-point scale. However, the control group did not receive a placebo supplement during the trial, which severely weakens the findings. A further trial showed that a 6-week intervention with valerian (600 mg/d) relieved emotional aspects of stress and improved sleep quality (from questionnaire data), although no control group was employed (Wheatley, 2001). Similarly, a number of placebo-controlled studies have demonstrated the effectiveness of kava for reducing symptoms of anxiety. A number of German studies reviewed by Bilia *et al.* (2002) demonstrated that 210 mg kava was as effective in reducing symptoms of anxiety as anti-anxiety agents such as benzodiazepines. Also, patients treated with 3 × 100 mg kava extract/d indicated improvements in anxiety symptoms after just 1 week (Lehmann *et al.* 1996). After 4–8 weeks, improvements in anxiety were accompanied by improvements in a clinical assessment score, and improved mood, with a further reduction in anxiety and clinical assessment score after 25 weeks of treatment (Lehmann *et al.* 1996; Volz & Kieser, 1997). These results were supported by a recent meta-analysis of six placebo-controlled trials in which treatment with kava was effective in treating the symptoms of anxiety in all studies (Pittler & Ernst, 2002). The mechanisms are thought to be associated with the modulation of serotonergic and glutamatergic systems, dopamine antagonism, and enhancement of the binding capacity of γ-aminobutyric acid receptors (Jorm *et al.* 2004).

Lastly, lemon balm (*Melissa officinalis*) is traditionally believed to convey general beneficial effects on the brain which is related to cholinergic receptor-binding properties of the extract. A dose of 1600 mg dried lemon balm leaf screened for positive cholinergic receptor-binding properties was associated with increased self-reported calmness for up to 6 h after ingestion (Kennedy *et al.* 2003). However, self-reported calmness also increased after 1 h following the ingestion of 300 mg of a non-binding extract (Kennedy *et al.* 2002*a*). Also, in a double-blind, placebo-controlled, randomised, balanced cross-over design a 600 mg dose of lemon balm was shown to ameliorate the negative mood effects of a 20 min stress task (that comprised a set of four concurrent cognitive and psychomotor tasks), significantly increase self-ratings of calmness, and reduce self-ratings of alertness (Kennedy *et al.* 2004). In addition, a significant increase in the speed of mathematical processing, with no reduction in accuracy, was observed after ingestion of a 300 mg dose (Kennedy *et al.* 2004). These studies suggest that lemon balm has potential stress-relieving properties, although further work should be performed to examine the efficacy of this extract for lowering physiological responses to stress.

Numerous studies in animals have examined the effects of ginkgo biloba and panax ginseng on the stress response. Rai *et al.* (2003) fed rats with either 100 mg ginseng/kg per d, 30 mg ginkgo biloba/kg per d, or a control diet for 3 d before acute (150 min) or chronic (150 min/d for 7 d) restraint stress. Exposure to acute and chronic stress resulted in hypertrophy of the adrenal gland and increased release of plasma corticosterone, indicating significant hyper-reactivity of the HPA axis. However, administration of ginkgo biloba significantly attenuated the acute increase in adrenal weight and corticosterone, whereas ginseng was effective in attenuating chronic increases in these stress parameters. The authors thus suggested that the mechanisms associated with the HPA modulatory activity of these two ingredients may differ. Ginkgo biloba may act on the adrenal cortical PBR and ginseng may restore an attenuated feedback response to the pituitary that is affected during chronic stress and responsible for the overproduction of corticosterone. These effects on the HPA axis during stress are supported by a number of other studies. Kim *et al.* (2003*a*) showed that pre-treatment with ginseng saponins (intraperitoneal injection of 5 or 20 mg/kg) significantly attenuated the immobilisation stress-induced increase in corticosterone in mice, although also raising non-stress baseline levels. Also, stress-induced increases in adrenaline, noradrenaline and corticosterone in rats were suppressed by 20 d oral treatment with 50 or 100 mg ginkgo biloba/kg per d (Rapin *et al.* 1994). Markus & Lammers (2003) showed a similar effect for reductions in corticosterone response to inescapable shock stress in rats, but only at a 2-week pre-treatment oral dosage level of 150 and not 50 mg ginkgo biloba/kg per d. However, rather surprisingly, the administration of 150, but not 50 mg/kg per d, also produced approximately a 100 % increase in plasma corticosterone in the non-stress group in comparison with the control non-stress animals. This increase in baseline corticosterone level under non-stress conditions appears to directly contradict previous research that showed a reduction in baseline corticosterone levels after administration of 50–100 mg ginkgo biloba/kg per d for 14 d in rats (Marcilhac *et al.* 1998). In relation to the mechanism, *in vivo* treatment of rats with ginkgolide B (the bioactive component of ginkgo biloba) has been shown to result in an 80 % reduction of adrenocorticotropic hormone-stimulated corticosterone production by adrenocortical cells and also transcriptional suppression of the PBR gene (Amri *et al.* 1997, 2003).

Lastly, an inhibitory effect of ginseng saponins on the restraint stress-induced plasma IL-6 release in mice has been demonstrated (Kim *et al.* 2003*b*). Interestingly, these effects were shown only when the saponins were administered via intraperitoneal but not intracerebroventricular injection,

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suggesting that the mechanism may be related to a peripheral action rather than at the brain. In the same study Kim *et al.* (2003*b*) demonstrated that the saponins significantly decreased noradrenaline- and/or adrenaline-induced increase of IL-6 in a macrophage cell line. Therefore, the inhibitory action of ginseng saponins against the stress-induced release of IL-6 may be mediated by blocking the catecholamines.

Micronutrients

Brody *et al.* (2002) conducted a parallel, double-blind placebo-controlled trial in 120 healthy subjects to examine the effect of a high dosage of sustained-release ascorbic acid (3 g/d for 14 d) on BP and cortisol response to a public speaking and mental arithmetic stress task (Trier Social Stress test). The subjects performed the stress task only once following the intervention period to avoid habituation effects. Compared with the placebo group, the ascorbic acid group demonstrated significantly lower systolic BP and diastolic BP responses to the stress task and faster post-stress salivary cortisol recovery, although overall cortisol response was similar. There were no differences in the placebo and ascorbic acid groups for the cortisol response to low-dose adrenocorticotropic hormone provocation, which excludes the possibility that adrenal responsiveness was modified. Instead, possible mechanisms may include modulation of noradrenergic activity and improvement of endothelial-dependent vasodilatation by the ascorbic acid supplement. For example, in a series of well-controlled infusion trials Lembo *et al.* (2000) demonstrated that the vascular hyper-responsiveness to noradrenaline is eliminated after arterial infusion of ascorbic acid in hypertensives, compared with controls. The vascular hyper-responsiveness is possibly due to an impairment of NO activity that is corrected by infusion of ascorbic acid. There is further evidence to suggest that NO activity could be impaired through noradrenaline-induced oxygen free radical production, thus suggesting that the effect of ascorbic acid may be linked to scavenger action on oxygen free radicals (Lembo *et al.* 2000). The efficacy of ascorbic acid in relation to improved endothelial function and NO activity in human subjects has also been demonstrated in a number of other high-quality publications (Levine *et al.* 1996; Solzbach *et al.* 1997; Taddei *et al.* 1998). That transient endothelial dysfunction has been demonstrated during mental stress (Ghiadoni *et al.* 2000; Spieker *et al.* 2002; Gottdiener *et al.* 2003) suggests that this may be a key mechanism. Thus, a high dosage of vitamin C appears to be potentially efficacious for lowering the biological response to stress.

Taylor *et al.* (2003) performed a placebo-controlled trial to examine the influence of 12 weeks' micronutrient supplementation (containing vitamins and trace elements) on the stress-induced inflammatory responses to examinations in twenty-two healthy medical students. Although there were significant differences in cytokine production (IL-6, TNF-α) between stressed and non-stressed subjects, the supplement had no effect on these inflammatory markers.

Lastly, the most convincing data with regards to micronutrients and mood relate to thiamine and Se (for reviews, see Benton & Donohoe, 1999; Benton, 2002).

n-*3 and* n-*6 Fatty acids*

Supplementation with *n*-3 and *n*-6 fatty acids is another possible candidate for modulating the stress response. Fish oils contain essential *n*-3 fatty acids in the form of EPA and docosahexaenoic acid (DHA) that have been associated with a significant reduction in cardiovascular events in patients with CHD (Kris-Etherton *et al.* 2003). Blackcurrant-seed oil and evening primrose oil are rich sources of essential *n*-6 fatty acid, commonly found in the form of γ-linolenic acid. Three human intervention trials have been conducted to examine the role of *n*-3 and *n*-6 fatty acids in lowering the stress response. Sawazaki *et al.* (1999) conducted a randomised, double-blind placebo-controlled trial in fourteen healthy volunteers to examine the effect of fish oil consumption on plasma catecholamine and cortisol responses to a chronic stress period. The volunteers were administered capsules containing either 1·5 g DHA/d or placebo containing mixed plant oil (a mixture of olive oil, rapeseed oil and soyabean oil) during a 9-week examination period that consisted of twenty stressful medical examinations. Although there was no difference in adrenaline levels between groups at the beginning or end of the supplementation period, noradrenaline levels were significantly reduced in the DHA group only. However, rather surprisingly, cortisol levels were significantly reduced in the placebo group and not the DHA group following the intervention. These data may be confounded by the use of olive oil in the placebo that contains bioactive compounds with functional health benefits (Kris-Etherton *et al.* 2002). In another study plasma adrenaline and cortisol responses to a 30 min stress task, consisting of mental arithmetic and Stroop tasks, were significantly blunted after 3 weeks of fish oil supplementation (1·1 g EPA/d and 0·7 g DHA/d) compared with the control response in seven healthy subjects (Delarue *et al.* 2003). Despite the apparently reduced activation of the adrenal gland by the fish oil intervention, BP and HR responses to the stress task were unaffected. However, it should be noted that this trial was not placebo-controlled and no attempt was made to control for the effects of task habituation that severely weakens the findings from this study. Deferne & Leeds (1996) conducted an 8-week randomised, placebo-controlled intervention in borderline hypertensives to examine the effect of blackcurrant-seed-oil supplementation on the cardiovascular response to a 5 min mental arithmetic task. Blackcurrant-seed oil is one of the richest sources of γ-linolenic acid and is unique in the fact that it contains appreciable amounts of α-linolenic and stearidonic acids, both members of the 3-series fatty acids. The intervention comprised either 500 mg pure blackcurrant-seed oil/d (containing 1 g *n*-6 and 950 mg *n*-3 oils) or 500 mg safflower-seed oil acting as the placebo. The results showed that BP reactivity was reduced by over 40 % in the blackcurrant-seed-oil group compared with subjects from the placebo group, although HR reactivity and baseline levels were unaffected by the intervention. One of the mechanisms responsible for this BP reactivity-lowering

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effect may be impairment of end-organ responsiveness. In a recent randomised, placebo-controlled and double-blinded trial, Monahan *et al.* (2004) showed that after 1 month of fish oil supplementation (3 g EPA/d and 2 g DHA/d) in healthy subjects the muscle sympathetic nerve activity response during an isometric handgrip stressor to fatigue was enhanced, despite no effects on the pressor response. Monahan *et al.* (2004) interpreted these findings as an impairment in end-organ responsiveness because increased muscle sympathetic nerve activity would be necessary to elicit the same pressor response in order to appropriately respond to the stressor. This interpretation is supported by previous studies demonstrating that 4–6 weeks' ingestion of *n*-3 fatty acids blunts forearm vasoconstrictor responses to intra-brachial infusion of noradrenaline (Chin *et al.* 1993; Mori *et al.* 2000).

Data from animal studies support the efficacy of DHA supplementation for reducing the noradrenaline response to stress. Rousseau *et al.* (1998) subjected rats to an intermittent feeding schedule to induce stress for 8 weeks, administering a semi-purified diet containing either 10 % sunflower-seed oil or a mixture of sunflower-seed oil and DHA. The stressed rats fed with the control diet demonstrated a significantly greater increase in cardiac noradrenaline levels following the stress period in comparison with the stressed DHA group. Also, the stressed control rats had a significantly elevated HR compared with unstressed rats and stressed rats given the DHA diet, although BP was unaffected by the dietary intervention in the stressed groups. However, the noradrenaline data are slightly difficult to interpret because unstressed rats that were supplemented with DHA appeared to have significantly higher levels of cardiac noradrenaline compared with the unstressed control group, which suggests that the stress-induced changes may have differed between groups due to differences in baseline noradrenaline. Some earlier animal work also studied the effects of EPA (intraperitoneal administration) on the cardiovascular response to 4 weeks' isolation stress in male rats (Mills & Ward, 1986). In contrast to the findings of Rousseau *et al.* (1998), this study demonstrated that the stress-induced rise in BP was attenuated but HR was increased in the EPA group, suggesting that EPA may induce peripheral vasodilatation.

The mechanisms that have been associated with the CVD risk-lowering benefits of fish oil supplementation include decreased risk of arrhythmias, decreased risk of thrombosis, decreased triacylglycerols and remnant lipoprotein levels, decreased rate of atherosclerotic plaque growth, improved endothelial function, lowered BP and reduced inflammatory responses (Kris-Etherton *et al.* 2003). Although current evidence for the stress reactivity-lowering effects of *n*-3 and *n*-6 supplementation remains equivocal, future trials should attempt to investigate whether any of the aforementioned mechanisms may be involved with a stress reactivity-lowering effect.

Discussion and conclusions

There appears to be a limited number of well-controlled studies that have examined the effects of nutritional intervention on psychobiological responses in human subjects and the evidence is equivocal for most of the dietary nutrients reviewed. The most promising effects were demonstrated in the nutritional interventions that used a high dosage of vitamin C and the *n*-3 fish oils. Although seemingly small, the BP stress-buffering effects demonstrated by these nutritional interventions may have significant implications for cardiovascular health. For example, Kamarck *et al.* (1997) have demonstrated that every standard deviation of stress-related BP responsiveness is associated with an additional 0·02–0·03 mm of carotid artery thickness, which is highly significant given that each incremental 0·1 mm of IMT is associated with an 11 % increased risk of acute myocardial infarction (Salonen & Salonen, 1993).

An inherent problem with the area of 'functional foods' research is that nutritional interventions which are administered to healthy participants often only have subtle effects. However, there are many psychobiological measures that have not been fully utilised in the studies reviewed here. For example, presently there are no studies that have examined the effects of nutritional interventions on haemodynamic responses to stress, such as platelet aggregates, endothelial function and inflammatory markers. Recent data have demonstrated a stress-induced increase in platelet aggregates (Steptoe *et al.* 2003) that may be an important psychobiological mechanism given that platelet monocyte count was recently shown to be a strong independent predictor of common carotid IMT and plaque formation (Chapman *et al.* 2004). Thus, future studies that employ a greater range of measures may provide stronger evidence for the psychobiological effects of functional foods.

Future human trials that examine the efficacy of nutritional interventions for lowering the acute stress response should pay particular attention to a number of key aspects of study design. These include controlling for task habituation, factors that cause inter-individual variability of the stress response (for example, socio-economic status, life events and social support, emotional and coping style, family history of hypertension and CVD, sleep, body fat and cholesterol levels, ethnicity, age, and sex), and providing evidence of nutrient uptake and compliance to the intervention. It is also essential that any intervention trial should be randomised, double-blind and placebo-controlled.

In conclusion, exaggerated biological responses to stress and psychosocial factors are associated with increased risk of CVD and hypertension. Interventions to lower excessive psychobiological responses will play an increasingly important role for the maintenance of health in a stressful environment. Dietary supplements appear to play some role in providing stress relief, although at present there is a lack of evidence from the scientific literature to substantiate a functional food claim. Nevertheless, research to identify key dietary supplements that can alleviate a range of potentially excessive and harmful psychobiological responses appears to be a developing area that should continue to receive attention in the future. Current recommendations for coping with stress should include consuming a healthy diet (supplemented with vitamin C and fish oils whilst reducing the intake of salt, caffeine, and sugary snacks), regular exercise, maintenance of optimal body fat and cholesterol

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levels, and adequate sleep. Interventions for lowering the stress response should be targeted at populations who appear to be most vulnerable to the effects of stress-induced ill-health, which include individuals with family history of CVD and hypertension, obese individuals, patients with high cholesterol, and black ethnic and lower socio-economic groups (Marmot *et al.* 1991; Light, 2001; Esler & Parati, 2004).

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