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POTENTIAL HEALTH EFFECTS OF CHAMPAGNE WINE CONSUMPTION

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Abstract

Epidemiological studies have suggested an inverse correlation between red wine consumption and the incidence of cardiovascular and neurodegenerative disorders. Although white wines are generally low in polyphenol content as compared to red wines, Champagne wines have been shown to contain relatively high amounts of phenolic acids that may exert protective cellular actions in vivo. In this study, we have investigated the potential cardioprotective and neuroprotective effects of Champagne wine. Our data suggest that a daily moderate consumption of Champagne wine may improve vascular performance via the delivery of phenolic constituents capable of improving NO bioavailability and the modulation of metalloproteinase. Moreover, Champagne wine intervention significantly increased spatial working memory in aged animals, whilst no improvement was observed in presence of alcohol. Together, these data suggest that polyphenols present in Champagne wine may induce cardioprotective and neuroprotective effects, delaying the onset of degenerative disorders.

Keywords: Champagne wine, cardiovascular disease, working spatial memory, polyphenols, brain

Introduction

Epidemiological studies have suggested an inverse correlation between the consumption of red wine and the incidence of cardiovascular disease and neurological disorders (Di Castelnuovo *et al.*, 2002; Orgogozo *et al.*, 1997). This protection, is mainly believed to be mediated by the ability of polyphenols present in the wine to exert anti-inflammatory properties (Rice-Evans and Miller, 1996) and to modulate signalling cascades that regulate nitric oxide production (Bastianetto, 2002) and neuronal survival (Schroeter *et al.*, 2002). Although white wines are generally low in polyphenol content, in particular flavonoids, compared to red wines, Champagne wine has been shown to contain relatively high amounts of phenolic compounds (Vauzour *et al.*, 2010). Moderate Champagne wine consumption has been shown to exert a number of effects *in vivo*, effecting peripheral serotonin and dopamine release (Boyer *et al.*, 2004) and increasing plasma vitamin A concentration (Cartron *et al.*, 2003). Champagne wine polyphenols have also be shown to protect cells against injury induced by peroxynitrite (Vauzour *et al.*, 2007a), a physiologically relevant oxidizing species which has been implicated in vascular wall pathology (van der Loo *et al.*, 2000) and neurodegeneration (Szabo *et al.*, 2007). However, thus far, there have been no studies investigating its consumption and changes in endothelial function and thus cardiovascular risk or improvement in memory. In the present studies, we have performed a human intervention trial in order to assess whether acute, moderate Champagne wine consumption is capable of modulating endothelial function in healthy human volunteers. Since improvements in blood flow in the brain may impact on memory in a number of ways (i.e increasing the delivery of oxygen to specific brain regions), we have also performed an animal study aiming at investigating the effects of a chronic Champagne wine intervention on spatial working memory. Together our data suggest that moderate Champagne wine consumption may help to improve both cardiovascular and dementia risks.

Materials and Methods

Human intervention: The study was conducted according to the guidelines laid down in the Declaration of Helsinki. Fifteen healthy male and female subjects were recruited from the University of Reading and surrounding area. The study was designed as a single blind, randomized, crossover intervention trial, where volunteers were asked to consume either 375 ml of Champagne wine (Chardonnay, Pinot Noir and Pinot Meunier, 12% alcohol) or a control matched for alcohol content, fruit sugars and acids. Subjects were randomly assigned to either the Champagne wine or control group and asked to consume the beverage within a 10 min period. Peripheral micro-vascular function was assessed by Laser Doppler imaging with iontophoresis (LDI), a validated technique which quantifies the vasodilator responses to 1% acetylcholine (ACh, endothelium dependent vasodilatation) and 1% sodium nitroprusside (SNP, endothelial independent vasodilatation), delivered trans-dermally. Following a washout period of 28 days, volunteers returned to the unit to complete the second arm of the study where the procedure above was repeated. Metalloproteinase were analyzed by gelatine zymography as previously described (Buache *et al.*, 2007). All biochemical parameters were assayed on an ILAB 600 chemistry analyzer (Instrumentation Laboratory, Warrington, UK) using enzyme based colorimetric tests supplied by Instrumentation Laboratory. Total Oxidative Capacity (TOC) was determined by a rapid enzymatic in vitro diagnostic assay obtained from Tatzber KEG (Höflein at the Danube, Austria).

Animal study*:* 3 groups of adult, male Wistar rats (n = 8 per group; Charles-River, France) were housed under a 12:12 light:dark cycle. All procedures were conducted according to the specifications of the United Kingdom Animals (Scientific Procedures) Act, 1986. The three intervention diets (placebo, ethanol 12% and Champagne wine (Chardonnay, Pinot Noir and Pinot Meunier, 12% alcohol)) used were analytically well characterized and contained a defined and characterized amount of phytochemicals and were as far as possible macro- and

micronutrient-matched. Rats were tested in a cross-maze apparatus as described previously (Williams *et al.*, 2008). Rats were given 3 test sessions on the cross-maze, one session administered immediately before supplementation was started (baseline), subsequent sessions were administered at 3 and 6 weeks. Following completion of the test, animals were sacrificed and brains were removed and hippocampal and cortical regions were dissected, snap-frozen in liquid nitrogen and stored at –80°C until analysis. Levels of proteins were assessed by Western immunoblotting as described previously (Vauzour *et al.*, 2007b)

Results and Discussion

Champagne wine promotes endothelium-independent vascular reactivity

Many epidemiological studies have suggested that a daily and moderate consumption of red or white wine is associated with a lower incidence of cardiovascular disease (Renaud and de Lorgeril, 1992). Many of the effects of red wine are compatible with the action of wine-derived polyphenols on endothelium-derived nitric oxide ($NO^{\bullet}$) production (Flesch *et al.*, 1998), whilst the white wine effects may result from the synergistic actions of polyphenols and other phenolic constituents on LDL oxidation and platelet function (Pignatelli *et al.*, 2006). In the present study, we show that Champagne wine consumption is capable of inducing acute vascular effects and in modifying levels of specific vascular active components. Indeed, consumption of Champagne wine was observed to induce an acute change in endothelium-independent vasodilatation at 4 and 8 hours post consumption ($p = 0.045$ and $p = 0.037$ respectively), whilst the alcohol matched control did not induce any changes in vascular reactivity. Although both Champagne wine ($p=0.030$) and the control ($p= 0.045$) induced an increase in endothelium-dependent vascular reactivity at 4h, there was no significant difference between the vascular effects induced by Champagne wine or the control. These observations are in agreement with previous studies which indicate that

moderate alcohol is capable of inducing an acute increase in blood flow in an endothelium-dependent manner (Tawakol *et al.*, 2004; Vlachopoulos *et al.*, 2003). However, we found that only the Champagne wine intervention was capable of significantly inducing an increase in endothelium-independent vasodilatation, which was maintained up to 8h post consumption. These data suggest that moderate Champagne wine consumption may enhance microvascular blood flow for a sustained period, through maintenance of local nitric oxide levels, in this case delivered via iontophoresis. These effects were also accompanied by an acute decrease in the concentration of matrix metalloproteinase MMP-9 (1h; $p<0.05$), a significant decrease in the plasma levels of oxidising species (6h; $p<0.05$) and an increase in urinary excretion of a number of phenolic metabolites. In particular, the mean total excretion of hippuric acid, protocatechuic acid and isoferulic acid were all significantly greater following the Champagne wine intervention compared to control intervention ($p < 0.001$). These phenolic metabolites may affect vascular function by improving local nitric oxide bioavailability by two potential mechanisms. Firstly, they may increase the local half-life of $NO^{\bullet}$ via reaction with reactive oxygen species, such as superoxide (Radi *et al.*, 2001). Secondly, phenolic metabolites, such as those excreted post Champagne wine consumption, may mimic NADPH oxidase inhibitors (Steffen *et al.*, 2007), such as apocynin thereby reducing the cellular production of superoxide and increasing the half-life of $NO^{\bullet}$, without any change in the rate of $NO^{\bullet}$ synthesis (Schewe *et al.*, 2008). Our data suggest that a daily moderate consumption of Champagne wine may improve vascular performance via the delivery of phenolic constituents capable of improving nitric oxide bioavailability and reducing matrix metalloproteinase activity.

Champagne wine improves working spatial memory

Epidemiological studies have suggested that moderate wine consumption may reduce the incidence of certain age-related neurological disorders including Alzheimer's disease

(Orgogozo *et al.*, 1997). Polyphenols may act to protect the brain in a number of ways, including by protection of vulnerable neurons, the enhancement of existing neuronal function or by stimulating neuronal regeneration (Youdim and Joseph, 2001). For example, red wine antioxidants were observed to protect hippocampal neurons against ethanol-induced damage (Assuncao *et al.*, 2007) and a moderate consumption of Cabernet Sauvignon attenuated Aβ-neuropathology in a mouse model of Alzheimer's disease (Wang *et al.*, 2006). There is also a growing interest in the potential of polyphenols to improve memory, learning and general cognitive ability (Vauzour *et al.*, 2008). In this study, we have investigated the effects of a chronic Champagne wine intervention on spatial working memory in aged animals (18 months), and have determined the molecular changes in the brain underlying these behavioural changes. The results indicated that Champagne wine intervention significantly increased spatial working memory in aged animals by 24.5 ± 3.4% ($p<0.01$), whilst no improvement was observed in presence of alcohol ($p>0.05$). Such observations are in agreement with previous studies demonstrating that chronic consumption of red wine unlike the ethanol solution alone, did not lead to a decline in hippocampal-dependent spatial memory (Assuncao *et al.*, 2007). However, Champagne wine, which is low in flavonoids, was also observed to improve spatial working memory. Such effects may be the result of other phytochemicals such as hydroxycinnamates, phenolic acids and phenol alcohol. We have previously reported the beneficial effect of such molecules in primary cortical neurons challenged with 5-*S*-cysteinyl-dopamine (Vauzour *et al.*, 2010) and peroxynitrite (Vauzour *et al.*, 2007a). Moreover, for any polyphenol to exert direct neuroprotective actions they must also undergo permeation of the blood brain barrier (BBB), something that has been reported for both flavonoids and hydroxycinnamates (Youdim *et al.*, 2004). However, whilst the ability of flavonoids to cross the BBB is believed to be dependent on lipophilicity, small phenolics are thought to transverse the BBB via amino acid transporters, such as has been

reported for 4-ethylcatechol (Meiergerd and Schenk, 1994). Furthermore, caffeic acid shares structural similarities with L-DOPA and, as such, may undergo BBB transport via catecholamine transporter systems.

In order to investigate the mechanisms underlying Champagne wine actions in the brain, we have assessed widespread changes in hippocampal and cortical protein expressions in response to the various interventions. Changes in the number of, and strength of, connections between neurons, via their specific interactions with the MAPK pathways, leading to an increase in neurotrophins such as BDNF through CREB activation were observed. It is well reported that flavonoids may exert cellular action by interacting with the PI 3-kinase, Akt/PKB and MAP kinase signalling pathways (Schroeter *et al.*, 2002). Smaller phenolics, such as caffeic acid or tyrosol, may also participate in cellular interactions of this nature (Nardini *et al.*, 2000), or may directly react with toxic intermediates, as has been observed for *p*-coumaric acid (Kerry and Rice-Evans, 1999). All together, these processes act to maintain the number and quality of synaptic connections in the brain, a factor known to be essential for efficient long term potentiation (LTP), synaptic plasticity and ultimately the efficient working of memory.

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