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Letter to the Editor

In vivo anti-diabetic potential of chlorogenic acid as a consequence of synergism with other phenolic compounds?

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A recent article by Zheng *et al.*[1], in the *British Journal of Nutrition*, reported that chlorogenic acid (CGA) and caffeine inhibit fat accumulation by regulating hepatic function in mice. The authors investigated the effect of CGA and caffeine in female Imprinting Control Region (ICR) mice, drawing the conclusion that these components of coffee reduced serum and hepatic lipid levels and led to the suppression of body-weight gain and fat accumulation in treated animals[1]. The evidence reported in the study suggested the hypothesis that CGA and caffeine exert their action by biological synergism and that, more generally, coffee polyphenols usually work through a synergistic mechanism. Comments, in brief, are discussed below.

Anti-obesity action of chlorogenic acid

CGA, namely (1*S*,3*R*,4*R*,5*R*)-3-{((2*Z*)-3-(3,4-dihydroxyphenyl)-prop-2-enoyl)oxy}-1,4,5-trihydroxycyclohexanecarboxylic acid, is one of the most frequently assumed polyphenolic compounds in the daily diet, due to its usual presence in a widely diffused beverage such as coffee. CGA was reported to act as an anti-obesity natural molecule; however, a recent paper on the effect of coffee on the prevention of type 2 diabetes has raised yet some criticism[2]. Despite the evidence reported by the authors[1], physiological supplementation (1·0 g/kg per d) in C57BL/6 male mice with CGA in combination with a high-fat diet did not reduce body weight compared with mice fed with the high-fat diet alone[3]. Yet, the anti-diabetic property of CGA along with caffeic acid or other phenolic acids and/or polyphenols was assessed in other experimental models, besides the above contribution by Zheng *et al.*[1,4,5]. CGA alone was reported to inhibit *in vitro* animal fatty acid synthase (FAS) or bacterial β-chetoacyl reductase (*EC* 1.1.1.100) in a concentration-dependent manner with respective half-maximal inhibitory concentrations (IC_{50}) of 94·8 and 88·1 μM[6]. This suggests that CGA can act directly on liver enzymes involved in metabolism. However, in the paper by Zheng *et al.*[1], the effect of this ester of caffeic acid and (−)-quinic acid on liver FAS was small, not statistically significant, while FAS activity was ameliorated by the addition of caffeine.

Mechanism of synergism and related complexity

The contribution of caffeine to improving the efficacy of CGA should stress the hypothesis that synergistic actions occur when two or more bioactive phenolic molecules share similar signalling or metabolic pathways. This may hamper any full elucidation of the biological effect of coffee polyphenols in different biological models. As a matter of fact, complexity pertains to the many, different issues regarding the biological activity of phytochemicals, fundamentally represented by raw-extract biochemistry, pharmacokinetics and bioavailability, in addition to the complex network of intracellular targets. In humans, gut absorption of CGA is at least one-third lower than that of other coffee-derived components, such as caffeic acid, but it exhibited high bioavailability in plasma[7–10]. Moreover, CGA exists in the form of a mixture of different caffeoyl-quinic acids, the commonest being probably 5-caffeoyl-quinic acid[11]. Such specification may be important because different isomers of caffeoyl-quinic acids exhibit different patterns of activity on liver enzymes[12]. As a matter of fact, all these observations lead to the suggestion that, at least in animal or *in vivo* models, the anti-diabetic and obesity-preventing activity attributed to CGA may occur when the polyphenol is associated with another phenolic acid or plant-derived alkaloid, such as the 1,3,7-trimethylpurine-2,6-dione reported by Zheng *et al.*[1], an occurrence that may also improve the bioavailability and biological action of CGA. Synergism between CGA and other components probably accounts for the action of CGA plus caffeine reported in the paper by Zheng *et al.*[1]. Caffeine improves glucose tolerance, insulin sensitivity and hyperinsulinaemia in C57BL/6J and ameliorates the inflammatory response of adipose tissue, which is notoriously involved in the metabolic syndrome[13]. In addition, CGA exerts inhibitory activity on hepatic glucose-6-phosphatase (*EC* 3.1.3.9), then influencing glucose homeostasis and contributing to the prevention of metabolic stress and type 2 diabetes[12]. The authors did not address any further hypothesis on the mechanism by which CGA and caffeine exerted an anti-diabetic action, except for a significant inhibition of liver FAS and increase in lipid β-oxidation.

Further comments and conclusions

In their paper, Zheng *et al.*[1] concluded that the observed enhancement of β-oxidation and suppression of lipogenesis were the major reasons for the reduction of fat accumulation and body-weight gain in mice. If true, lipid β-oxidation in hepatic and adipose tissue may be enhanced by the request

of lipids from tissues, consequently leading to lipolysis in adipose tissue and changes in the plasma lipid profile. Unfortunately, the paper by Zheng *et al.*[1] did not fully elucidate this issue by evaluating, for example, the serum lipoprotein profile. In this respect, inhibition of hepatic *EC* 3.1.3.9 by CGA should yet lead to an increase in lipogenesis, without affecting VLDL production and cholesterol synthesis by the liver[13]. Therefore, the effect reported by Zheng *et al.*[1] on serum lipids might not be associated with the inhibition of liver glucose-6-phosphatase by CGA, but most presumably caused by other mechanisms. While synergism appears to possibly explicate the observed reduction in FAS activity, the effect of caffeine appears to overwhelm the action of CGA on carnitine acyltransferase (*EC* 2.3.1.21) and acyl-CoA-oxidase (*EC* 1.3.3.6), namely that the enhancement of the activity of enzymes involved in lipid oxidation in the mitochondria and peroxisomes should be attributed principally to caffeine, at least as emerging from the paper by Zheng *et al.*[1]. In addition, CGA may enhance the inhibitory effect on serum lipids, as it was reported that in Zucker rats, it lowers plasma cholesterol and TAG levels[14], thus contributing to the overall observed effect[1]. Both CGA and caffein shared the same liver enzyme system, which targeted to modulate glucose and lipid homeostasis. The interesting study by Zheng *et al.*[1] raises many questions about how these components act in coffee, where many other polyphenolic substances, i.e. kaempferol, ferulic acid and caffeic acid, may participate in the synergistic/antagonistic mechanism characterising most of the plant-derived raw extracts. While a possible purpose of such studies is to highlight particular molecules as effective prodrugs against the metabolic syndrome, we should not forget that molecules in a complex mixture behave quite far from our *in vitro* and animal models, due to the many reasons such as synergism, gut microflora modification, adsorption rate, bioavailability and different cell responses to the indicated molecule.

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