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Pharmacokinetics of caffeine and its metabolites in plasma and urine after consuming a soluble green/roasted coffee blend by healthy subjects

Sara Martínez-López, Beatriz Sarriá, Gema Baeza, Raquel Mateos, Laura Bravo-Clemente *

Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition (ICTAN), Spanish National Research Council (CSIC), José Antonio Novais 10, 28040 Madrid, Spain

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ABSTRACT

Coffee is widely consumed worldwide; therefore, the methylxanthines contained in coffee, mainly caffeine (CF), are among the most abundant bioactive compounds in our diet. In the present work, the bioavailability and metabolism of methylxanthines in a commercial soluble green/roasted coffee blend was studied. After a 3-day restriction of methylxanthine-containing foods, fasting healthy subjects (12 men and women) consumed the coffee product containing 70.69 mg CF and 0.119 mg theobromine (TB). Plasma samples were taken before ($t = 0$ h) and after coffee consumption at different time points (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 9, 10 and 12 h). Urine was collected at baseline (−2–0 h) and at different intervals (0–2, 2–5, 5–8, 8–12 and 12–24 h). Samples were analyzed by HPLC-DAD and LC–MS-QToF, and pharmacokinetic parameters were calculated. CF was the main methylxanthine found in plasma ($C_{max} = 10.50$ μM, $T_{max} = 1.2$ h). In addition, seven methylxanthines and methyluric acids were detected between 0.5 and 12 h after coffee intake, paraxanthine (PX) being the major metabolite ($C_{max} = 3.36$ μM), followed by 1-methyluric acid (1-MU; $C_{max} = 1.44$ μM) and 1-methylxanthine (1-MX; $C_{max} = 1.27$ μM), identified in plasma samples for the first time. In 24 h urine, eleven methylxanthines and methyluric acids were detected, 1-MU being the major metabolite ($C_{max} = 150.52$ μM, $T_{max} = 12$ h) amounting to 67.7% of the total urinary metabolites. In conclusion, a rapid absorption, metabolization and excretion of caffeine and its derived methylxanthines and methyluric acids have been observed after consumption of a green/roasted coffee product.

1. Introduction

Coffee is one of the most widely consumed beverages worldwide. Its distinctive aroma and its well-known stimulating effects have made it one of the most popular beverages. Coffee can be consumed as an infusion or mixed with milk, and often sugar, chocolate, cream or liquor are added depending on cultural traditions and individual preferences. Coffee consumption varies widely between countries: in 2011 Switzerland and Scandinavian countries showed the highest consumption, over 6 kg/person/year. The present consumption in Spain is 4.2 kg/person/year (www.ico.org).

Coffee is rich in different bioactive compounds, specially methylxanthines and polyphenols. Caffeine is the major methylxanthine in coffee, this beverage being the main dietary source of this bioactive compound. In coffee seeds, caffeine content ranges between 10 and 20 g/kg together with trace amounts of theobromine and theophylline (Koleva, van Beek, Soffers, Dusemund, & Rietjens, 2012). In soluble roasted coffee, caffeine concentrations as high as 771.4 μg/mL have been reported, with minor amounts of the dimethylxanthines theobromine (11.50 μg/mL) and theophylline (0.06 μg/mL) (Aragao, Veloso, Bispo, Ferreira, & de Andrade, 2005). Alonso-Salces, Guillou, and Berrueta (2009) observed caffeine concentrations between 10.5 and 17.4 g/kg dry weight in Arabica (*Coffea arabica*) green coffee beans. In addition to agricultural and geographical factors, methylxanthine content in coffee depends on the mode of preparation, with instant coffee having higher caffeine concentrations than filtered coffee (Samanidou, Tsagiannidis, & Sarakatsianos, 2012). In terms of consumption, a cup of instant coffee (225 mL) contains between 60 and 85 mg of caffeine, whereas a cup of espresso coffee (28 mL) shows between 30 and 50 mg of caffeine (Crozier, Stalmach, Lean, & Crozier, 2011). Concentration of phenolic compounds in green coffee beans may range between 6 and 10% (dry weight) (Chu et al., 2009), being mostly hydroxycinnamic acids (chlorogenic acids). Other minor components such as terpenoids (cafestol and kahweol) and potassium have been found in 0.6% and 2.5% dry matter, respectively (Bonita, Mandarano, Shuta, & Vinson, 2007).

In the past, coffee consumption was associated with unfavorable effects on vascular function, increasing blood pressure, plasma cholesterol or LDL oxidation in healthy humans (Bonita et al., 2007). However, the negative effects associated with coffee consumption have been questioned and its perception changed in recent years. In 2008 the World Anti-Doping Agency (WADA) excluded caffeine from the

* Corresponding author at: Department of Metabolism and Nutrition, Institute of Food Science, Technology and Nutrition (ICTAN), Spanish National Research Council (CSIC), C/José Antonio Novais 10, 28040 Madrid, Spain. Tel.: +34 915445607.
E-mail address: lbravo@ictan.csic.es (L. Bravo-Clemente).

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"Prohibited List—International Standards". An epidemiological study suggested that cardiovascular benefits are associated with moderate coffee consumption (<6 cups/day; Bonita et al., 2007). A meta-analysis based on five epidemiological studies has recently shown that moderate consumption of coffee (4 servings per day) was inversely associated with the risk of heart failure (Mostofsky, Rice, Levitan, & Mittleman, 2012). Additionally, coffee also seems to reduce inflammation (Kempf et al., 2010), although further research is necessary to better understand this effect (Frost-Meyer & Logomarsino, 2012). Recently, other authors have pointed to beneficial health effects such as decreasing the risk of type 2 diabetes mellitus in overweight volunteers who consumed 5 cups/day (Weedick et al., 2011) or pain alleviation in patients with advanced cancer (Suh et al., 2013).

Although most of the health effects indicated above have been attributed to coffee's polyphenol content (Bravo, Sarriá, Gómez-Juaristi, Martínez-López, & Mateos, 2010), methylxanthines may also play a role, since these compounds have already shown an improvement in antioxidant status in humans (Azam, Hadi, Khan, & Hadi, 2003; Gómez-Ruiz, Leake, & Ames, 2007), as well as vasodilation and cardiac-stimulation (Riksen, Smits, & Rongen, 2011) and HDL-cholesterol raising effects (Neufingerl, Zebregs, Schuring, & Trautwein, 2013). The most widely known positive effects of caffeine are its stimulatory effect on the central nervous system, improved physical performance and alertness, and its ability to enhance mood and well-being feeling (Kaplan et al., 1997), equally affecting habitual consumers and abstainers (Haskell, Kennedy, Wesnes, & Scholey, 2005).

Health effects associated with coffee consumption largely depend on the bioavailability and biotransformation of its bioactive components in the organism. Pathways of caffeine metabolism were recently reviewed by Arnaud (2011) and are presented in Fig. 1. Caffeine (CF, 1,3,7-methylxanthine) is completely absorbed in the gastrointestinal tract and rapidly reaches the liver, where it is metabolized by cytochrome P450 yielding three major dimethylxanthine metabolites: paraxanthine (PX, 1,7-methylxanthine), theobromine (TB, 3,7-methylxanthine) and theophylline (TP, 1,3-methylxanthine) in the proportion of 80:12:7 (Atia, York, & Clark, 2009), and to a lower extent to trimethylated urate,

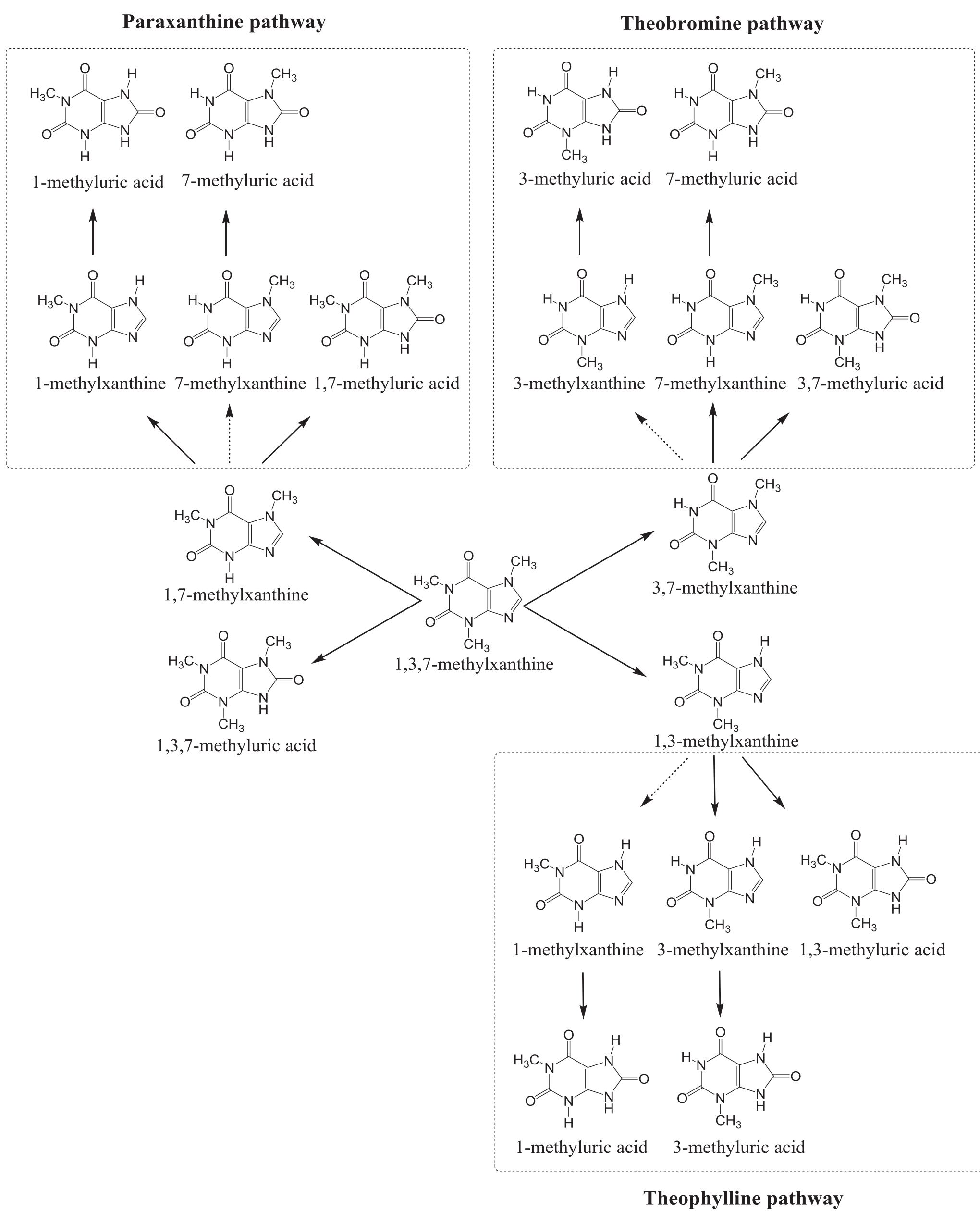

Fig. 1. Metabolic pathways of caffeine and its metabolites.