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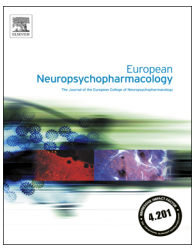

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Genetic determinants of cognitive responses to caffeine drinking identified from a double-blind, randomized, controlled trial

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Abstract
The widely observed between-subject variability in cognitive responses to coffee may have a genetic basis.
We evaluated cognitive responses to caffeine throughout three complex cognitive tasks assessing different subdomains of attention, namely Alerting and Orienting (Categorical Search Task) and Executive Control (Stroop Task and Eriksen Flanker Task). We explored whether they are influenced by gene variants affecting adenosine metabolism or catecholamine receptors.
We recruited 106 healthy male subjects who were administered, in a double-blind design, 40 mL of either a decaffeinated coffee preparation plus 3 mg/kg caffeine (caf) or the corresponding vehicle (decaf). The protocol was repeated 24 h later with the alternative preparation. Cognitive tasks

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were performed between 30 min and 2 h after caf or decaf administration. Each subject underwent ambulatory blood pressure monitoring for 2 h. Blood samples were collected for genetic evaluations and for plasma caffeine and catecholamines measures.
We found a significant reduction of reaction times in two of the cognitive tasks (Categorical Search Task and Stroop Task) after caf compared with decaf, indicating that caffeine, on average, improved the attention level in the domains under investigation. We also found, however, a great inter-individual variability in the cognitive performance responses to caffeine. In exploring genetic sources for such variability, we found a relation between polymorphisms of adenosine A2A and the caffeine effects on the attentional domains of Orienting and Executive control.
In conclusion, variability in the attentional response to coffee may be partly explained by genetic polymorphisms of adenosine and adrenergic receptors.

1. Introduction

Coffee, the most popular beverage consumed in the world, is a mixture of hundreds of chemical substances, the primary of which is caffeine, with well-known cardiovascular and psychoactive stimulatory and metabolic effects. The main mechanism of action of caffeine is to antagonize adenosine receptors (Ribeiro and Sebastiao, 2010); a secondary effect is the inhibition of phosphodiesterases (Ribeiro and Sebastiao, 2010), with the subsequent accumulation of cyclic AMP and an intensification of the effects of catecholamines (Robertson et al., 1978). Such properties translate, in most people, in a cognitive response (Lieberman, 2001), which includes increased alertness and attention (Einother and Giesbrecht, 2013; Lieberman et al., 1987), and in a complex cardiovascular response, mainly consisting of an increase in blood pressure (BP) (Riksen et al., 2009). However, large inter-individual variations in acute responses to caffeine have been reported, with subjects totally indifferent to even a large amount of coffee ingestion, and subjects deriving profound cognitive and cardiovascular consequences to coffee drinking (Chait, 1992; Evans and Griffiths, 1991; Wu et al., 2009). Particularly concerning psychoactive responses, controlled studies have found conflicting results. Both positive and null effects of caffeine on cognitive performance have been reported, especially in complex tasks assessing higher-order processes involved in the active monitoring and coordination of behavior (i.e., executive control processes) (Deslandes et al., 2005; Einother and Giesbrecht, 2013; Kenemans et al., 1999). Moreover, while caffeine does not affect mood in many subjects, others experience increased anxiety (Chait, 1992; Evans and Griffiths, 1991).

The variability observed in the cardiovascular and psychoactive responses to coffee drinking is likely in part due to tolerance (Colton et al., 1968), but may also be – to some extent – genetically determined, due to inter-individual differences in caffeine metabolism (Cornelis et al., 2006; Sachse et al., 1999), or caffeine effectors, such as the adenosine (Alsene et al., 2003; Childs et al., 2008; Rogers et al., 2010; Yang et al., 2010) or adrenergic receptors (Happonen et al., 2004; Renda et al., 2012). Indeed, cytochrome P450 1A2 (CYP1A2) polymorphism, affecting caffeine metabolism, has been related to cardiovascular risk in coffee drinkers: slow caffeine metabolizers (subjects with the CYP1A2*1F allele), with decreased enzyme inducibility, in turn resulting in impaired caffeine metabolism, were found to be at increased risk of hypertension (Palatini et al., 2009) and myocardial infarction (Cornelis et al., 2006) compared with rapid caffeine metabolizers (carrying the wild-type A2*1A allele). Furthermore, many of caffeine psychoactive effects are thought to be mediated by the two adenosine receptor subtypes A1 and A2A (Svenningsson et al., 1997), both expressed in the human brain (Fredholm et al., 2000), for which genetic variants have been described. For example, genetic mutations in the adenosine receptor A2A (ADORA2A) gene have been associated with anxiety (Alsene et al., 2003; Childs et al., 2008; Rogers et al., 2010) and with blood pressure changes (Renda et al., 2012) induced by caffeine. Recent data have also suggested that a common genetic variant in ADORA2A, with a role in sleep induction and sleep patterns in humans, contributes to subjective and objective individual sensitivity to caffeine on sleep (Retey et al., 2007). Finally, the effect of caffeine may be mediated by catecholamines, the levels of which increase after caffeine, and catecholamine receptors, for which genetic variants also exist, contributing to the inter-individual variability of some cardiovascular effects (Renda et al., 2012).

After reporting on genetic determinants of BP responses to caffeine (Renda et al., 2012), here we report on genetic determinants of attentional responses to caffeine, which are still unexplored.

2. Experimental procedures

2.1. Study aims

We aimed at gaining insight on the genetic determinants of cognitive responses to caffeine. To this purpose, we used three cognitive tasks assessing different subdomains of attention, namely Alerting, Orienting and Executive control (Posner and Petersen, 1990). Alerting pertains to achieving and maintaining a state of high sensitivity to signals occurring at unexpected times or in unknown locations; orienting pertains to the ability to selectively direct attention to regions of space; and executive control refers to the mechanisms for detecting and resolving conflicts and interferences among thoughts, feelings and responses.

We evaluated whether behavioral performances after the intake of a caffeinated beverage, compared with a decaffeinated one, is affected by the genetic asset of adenosine metabolism or genetic variants of catecholamine α- and β-receptors. For adenosine metabolism we considered a polymorphism of the adenosine receptor A2A (ADORA2A Tyr361Tyr; for correspondences among various