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REVIEW

Genetics of caffeine consumption and responses to caffeine

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Abstract
Rationale Caffeine is widely consumed in foods and beverages and is also used for a variety of medical purposes. Despite its widespread use, relatively little is understood regarding how genetics affects consumption, acute response, or the long-term effects of caffeine.
Objective This paper reviews the literature on the genetics of caffeine from the following: (1) twin studies comparing heritability of consumption and of caffeine-related traits, including withdrawal symptoms, caffeine-induced insomnia, and anxiety, (2) association studies linking genetic polymorphisms of metabolic enzymes and target receptors to variations in caffeine response, and (3) case-control and prospective studies examining relationship between polymorphisms associated with variations in caffeine response to risks of Parkinson's and cardiovascular diseases in habitual caffeine consumers.
Results Twin studies find the heritability of caffeine-related traits to range between 0.36 and 0.58. Analysis of polysubstance use shows that predisposition to caffeine use is highly specific to caffeine itself and shares little common disposition to use of other substances. Genome association studies link variations in adenosine and dopamine receptors to caffeine-induced anxiety and sleep disturbances. Polymorphism in the metabolic enzyme cytochrome P-450 is associated with risk of myocardial infarction in caffeine users.
Conclusion Modeling based on twin studies reveals that genetics plays a role in individual variability in caffeine consumption and in the direct effects of caffeine. Both pharmacodynamic and pharmacokinetic polymorphisms have been linked to variation in response to caffeine. These studies may help guide future research in the role of genetics in modulating the acute and chronic effects of caffeine.

Keywords Caffeine · Adenosine · Dopamine · Genetic polymorphism · *CYP1A2* · Parkinson's cardiovascular disease

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Introduction

Caffeine is the most commonly consumed psychoactive substance in the world. Nearly 90% of US adults consume caffeine in forms of coffee, tea, or other caffeinated food products (Frary et al. 2005). Caffeine's popularity worldwide can be attributed to its ability to promote wakefulness, enhance mood and cognition, and produce stimulatory effects (Haskell et al. 2005; Lieberman et al. 2002). It is used clinically to treat premature neonatal apnea and as an analgesic adjuvant (Migliardi et al. 1994; Schmidt et al. 2007). Caffeine causes diuresis, bronchodilatation, and a rise in systolic blood pressure in nonhabitualized subjects (Benowitz 1990; Mosqueda-Garcia et al. 1993). At low doses, its psychological effects include mild euphoria, alertness, and enhanced cognitive performance (Lieberman et al. 1987), but at higher doses, it produces nausea, anxiety, trembling, and jitteriness (Daly and Fredholm 1998). Tolerance to its acute effects develops rapidly

(Evans and Griffiths 1992; Robertson et al. 1981), such that the effects of caffeine in habitual consumers are quite different from caffeine-naïve individuals. Physical dependence can develop, and withdrawal symptoms occur upon discontinuation of regular caffeine use (Griffiths and Woodson 1988). The effects of chronic consumption are less clear. Long-term use of caffeine has been associated with an increased risk of cardiovascular diseases (Hartley et al. 2000; Klatsky et al. 1990) but a decreased risk in neurodegenerative disorders (Ascherio et al. 2001; Maia and de Mendonca 2002; Ross et al. 2000).

There are pronounced individual differences in response to caffeine. For example, some individuals are susceptible to its anxiogenic effects (Silverman and Griffiths 1992) and others to caffeine-induced sleep disturbances and insomnia (Bchir et al. 2006). Caffeine can aggravate anxiety and precipitate panic attacks in patients with anxiety and panic disorder, which often results in decreased consumption in these individuals (Bruce et al. 1992; Charney et al. 1985; Lee et al. 1985; Nardi et al. 2009). Individual differences in responses to caffeine may occur at the metabolic (pharmacokinetic) or at the drug-receptor level (pharmacodynamic), and they can contribute to the quality and magnitude of direct drug effects as well as to consumption of the drug. Likewise, certain individuals may be more vulnerable to the long-term negative health effects of caffeine. For example, while the pressor effects of caffeine attenuate rapidly in most consumers upon repeated intake, tolerance remains incomplete in certain subjects (Farag et al. 2005; Lovallo et al. 2004). Hypertensive subjects have been shown to be more likely to experience rise in blood pressure after caffeine consumption even with repeated administration (Nurminen et al. 1999). It is likely that several factors contribute to individual differences in responses to caffeine, including demographic and environmental factors such as age, other drug use, circadian factors, and sleep hygiene. One important source of variability that has received some attention in recent years is genetic predisposition.

There is growing evidence that individual differences in caffeine response or caffeine consumption are related to genetic factors. Genetic factors may influence responses to caffeine directly, by altering acute or chronic reactions to the drug, or indirectly, by affecting other psychological or physiological processes that are related to the drug effect, such as sensitivity to anxiety, rewarding, and reinforcing effects of substances in general, or related personality traits. Finally, genes can also alter the body's adaptive responses to long-term caffeine use. The biological mechanisms of these possible sources of variation likely involve interactions at multiple sites.

In the three sections of this paper, we will review genetic studies associated with variations in caffeine effects. First, we will consider twin studies that examine the contributions of genetics to consumption of caffeine and its effects. Second, we will review studies that have identified pharmacokinetic and pharmacodynamic variations that affect acute response. Third, we will discuss evidences that genetic factors influence long-term effects of caffeine. Finally, we will discuss the clinical significance and possible future research directions.

Genetics and caffeine response

Twin studies

Twin studies provide powerful evidence for the heritability of traits including response to caffeine. Heritability refers to degree of genetic influence and can vary from 0 (not heritable) to 1 (completely inherited). Twin studies estimate heritability by comparing monozygotic twins, who share the common familial environment and the same genes, to dizygotic twins, who also share common familial environment but only half of the genetic material. The contribution of different sources of variation to an observable trait can then be derived using biometric modeling, which attributes the observed variations to genetic, common environmental, and unique environmental sources (for detailed description of modeling techniques used in twin studies, see Kendler 1993; Neale and Cardon 1992). In addition to calculating the heritability of traits related to caffeine sensitivity and use, models can account for the influence of age, environmental factors, and gender differences on response and consumption patterns. Table 1 summarizes twin studies investigating caffeine-related traits. Broadly, two types of outcomes are assessed in these studies: consumption level and direct effects such as toxicity, tolerance, withdrawal, and caffeine-induced sleep disorders. These studies find heritability of caffeine traits from tea or coffee consumption to vary from 0.30 to 0.60 in different populations. They confirm the possibilities of caffeine consumption inheritance in twins without identifying the individual genes responsible for such differential inheritance pattern. This section will review studies that investigate the impact of genetics on consumption levels, direct effects, and the specificity of these inherited traits to caffeine.

Several twin studies have shown significant contribution from genetic sources in determining caffeine intake. One such study assessed the level of caffeine consumption in female twins using average daily consumption of coffee, caffeinated tea, and caffeinated soda via individual interviews (Kendler and Prescott 1999). Using biometric model fitting, overall caffeine consumption was found to have a heritability of 0.43. Heavy consumption, defined as >625 mg of caffeine daily, had a heritability of 0.77. Two twin studies of male veterans examined coffee consumption

Table 1 Twin studies on heritability of caffeine-related traits

Study	Number	Sex	Group	Traits measured	Heritability	Notes
Carmelli et al. (1990)	9,920	♂	US veterans Caucasian	Cups of coffee per day	0.36	Adjusted for smoking and alcohol
Hettema et al. (1999)	7,728	♂+♀	Virginia Caucasian	Average daily consumption of coffee and tea. Also measured tobacco and alcohol use	0.57 (♂) 0.58 (♀)	0.67 caffeine specific 0.72 caffeine specific
Kendler and Prescott (1999)	1,934	♀	Virginia Caucasian	Caffeine (coffee, tea, soda) use, heavy use (>625 mg), toxicity, tolerance, withdrawal symptoms	0.40 0.45 0.35 0.43 0.77	Tolerance Toxicity Withdrawal Overall use Heavy use
Kendler et al. (2007)	4,865	♂+♀	Virginia Caucasian	Caffeine dependence symptoms (sum of symptoms of tolerance and withdrawal during maximum) during period of maximum caffeine intake	0.34	0.91 caffeine specific
Kendler et al. (2008)	1,796	♂	Virginia Caucasian	Yearly levels of caffeine use from adolescent to adulthood Also measured alcohol, cannabis, nicotine use	0.30–0.45	Heritability rises from age 9–14 and then remains stable
Laitala et al. (2008)	10,716	♂+♀	Finland	Daily coffee consumption in 1975 and 1981	0.56 0.45	In 1975 In 1981
Luciano et al. (2005)	8,167	♂+♀	Australia	Daily coffee and tea consumption; preference of coffee over tea	0.51 0.26 0.48 0.42	Coffee Tea Total caffeine Preference for coffee over tea
Luciano et al. (2007)	7,616	♂+♀	Australian	Coffee-attributed insomnia	0.40	
Swan et al. (1997)	712	♂	US veterans Caucasian	Consumption of coffee (cups per day), cigarettes, alcohol	0.36 0.28	Coffee; 0.72 coffee specific Common factor for joint substance use
Swan et al. (1997)	4,593	♂	US veterans Caucasian	Heavy consumption of coffee (>5 cups/day), cigarettes, alcohol	0.51 0.41	0.59 coffee specific common factor for coffee and smoking
Teucher et al. (2007)	3,262	♀	UK	Food frequency questionnaire (servings of coffee calculated)	0.41	
Vink et al. (2009)	4,495	♂+♀	The Netherlands	Coffee consumption and preference over tea	0.39 0.62	Coffee Coffee preference

Heritability is calculated by partitioning sources of variation into genetic and common factors using twin modeling. Common factor refers to heritability that is shared across substances. Further details are provided in text and can be found in the individual papers

using cups of coffee per day as outcome measure and found heritabilities of 0.36–0.38 (Carmelli et al. 1990; Swan et al. 1996). These values lay in range with the results from studies on other twin populations using similar modeling techniques, with results ranging from 0.38 to 0.58 (Hettema et al. 1999; Laitala et al. 2008; Luciano et al. 2005; Vink et al. 2009).

Genetic contribution to caffeine consumption changes through different stages in life. A retrospective study evaluating the use of caffeine in males from early adolescence through middle adulthood examined the number of caffeinated drinks over the years as recalled by the subjects. By decomposing the variation source into additive genetic, familial environmental, and unique environmental factors and tracing the caffeine intake between the ages of 9 and 41, the best-fit model showed that family environment accounts for most of the variance in caffeine use from 9 to 14 years of age, but declined afterward and from late adolescence until middle adulthood genetic contribution accounted for 0.30–0.45 of the variance (Kendler et al. 2008).

It appeared, therefore, that genetic contribution became more pronounced throughout adolescence and then stabi-

lized during adulthood. Similarly, a study of coffee consumption in Finnish twins found that coffee consumption was affected by a set of genetic factors that was stable over time in adults (Laitala et al. 2008). Self-reported questionnaire was used to ascertain subjects' coffee consumption in 1975 and again in 1981. There was a moderate correlation for consumption between the two time points (0.58 in men and 0.55 in women), while the genetic factors affecting coffee consumption remained stable at 0.83 (women) and 0.84 (men).

Another process by which genetics can influence caffeine response is by predisposing individuals to certain positive or negative effects, such as susceptibility to its withdrawal symptoms or its effects on sleep. Kendler and Prescott (1999) examined the extent to which genetics influence individual sensitivity to caffeine toxicity, tolerance, and withdrawal in female twins. Outcome measures were assessed via individual interviews asking for history of jitteriness, need for increased dosage, and withdrawal symptoms per DSM-IV criteria. Using the same modeling method as described above, the heritability for toxicity, tolerance, and withdrawal was estimated to be 0.45, 0.40, and 0.35, respectively. A study in Australian twins investigated the inheritance of caffeine-attributed sleep disturbances and its relation to other types of sleep disturbances (Luciano et al. 2007). To test the degree of overlap between coffee-attributed insomnia and other types of insomnia, the study applied multivariate analysis with Cholesky decomposition to account for environmental and genetic variances. On average, women reported slightly higher level of caffeine-induced insomnia and greater sleep disturbances in general than men. The overall heritability of coffee-attributed insomnia was found to be 0.40, with three quarters of the genetic variance unrelated to the general sleep factor. Furthermore, the likelihood polychoric phenotypic correlations between coffee-attributed insomnia to other types of insomnia ranged only from 0.23 to 0.39. These values were lower than the intercorrelation values among noncoffee sleep disturbances, which ranged from 0.40 to 0.79. Together, these results suggested that genetic mechanisms for caffeine-attributed sleep disturbance differ from those for other types of sleep disturbances.

One fundamental question arising from genetic studies is whether the inherited factor predisposes an individual specifically to caffeine, or if it underlies a broader disposition to substance use in general. Epidemiological studies indicate that smokers drink more coffee than nonsmokers (Swanson et al. 1994), but it is not clear whether these associations are related to genetic factors or to drug interactions, social conditioning, or other variables. One approach to solving this question is to correlate the use of caffeine to other drugs and using the common pathway model and mapping the genetic contribution to a common joint use factor and a substance-specific factor (Kendler et al. 1987). Using this technique, Kendler and Prescott (1999) found that heritability for caffeine use was not correlated to heritability for alcohol, nicotine, and illicit drug use. However, other studies found that the heritability for coffee use overlapped with that of nicotine and alcohol, though 0.72 of the total heritability was specific to caffeine, which was considerably higher than that for nicotine and alcohol (Hettema et al. 1999; Swan et al. 1996). Another study assessed inherited specificity for dependence and abuse liability to cannabis, cocaine, alcohol, nicotine, and caffeine lifetime in twin pairs (Kendler et al. 2007). Scores were calculated by summing total symptoms for abuse and dependence using the DSM-IV criteria for alcohol, cocaine, and cannabis; the Fagerström Test for Nicotine Dependence for nicotine; and the sum of symptoms of tolerance and withdrawal as the measure for caffeine dependence. Tolerance for caffeine was defined as the need to use more to obtain the same effect or diminished effect with the same amount. Multivariate modeling was employed to determine the degree which environmental and genetic influence was shared across substances. Analyzing patterns of caffeine tolerance and withdrawal in conjunction with that for other substances showed that genetic heritability toward caffeine dependence did not correlate with heritability for dependence or abuse of illicit substances such as heroin and cocaine (Kendler et al. 2007). Instead, the best-fit model composed of the genetic heritability from two attributes, one for licit and one for illicit substances. Genetic liability toward caffeine tolerance and withdrawal came mainly from the licit factor, receiving little contribution from the illicit substance factor, and was highly specific to caffeine. The symptoms of caffeine tolerance and withdrawal were similar for males and females, both a heritability of 0.34. While these studies reached slightly different conclusions about the joint heritability for coffee, smoking, and alcohol use, all of them found the genetic contribution to caffeine and coffee consumption to be highly substance specific, indicating that the mechanisms predisposed individuals in a way that was unique to caffeine.

Among studies of dietary sources of caffeine, the measure used for assessing daily caffeine intake is important. Preference for certain sources can have social or cultural bases, which can confound the genetic effects. Most of the studies used coffee alone or a combination of tea or coffee as dietary intake measure of caffeine, though some studies have attempted to distinguish coffee and tea drinking. In one study, daily coffee and tea drinking was compared in Australian twins, and a preference score for tea or coffee was calculated. Heritability was estimated to be 0.51 for coffee consumption and 0.26 for tea consumption (Luciano et al. 2005). The analyses revealed several underlying differences in patterns of coffee and tea

consumption. Unlike models for coffee and caffeine consumption, whose best-fit models consist of genetic and unique environmental factors with no contribution from common environment, tea consumption had a modest common environment contribution. The lower heritability for tea drinking could be due to the lower caffeine content of tea or could signify different populations of tea versus coffee drinkers. However, there was no correlation between coffee preferences and the number of caffeinated drinks consumed per day, even though tea averages lower caffeine content per cup than coffee. The data suggested therefore that environment plays a larger role in tea than coffee consumption and that social environment affects tea and coffee drinking patterns differently.

Certain food preferences are heritable, and this appears to be especially true of foods such as coffee that have strong tastes. A food preference study in UK twins used principle component analysis to show that preference for coffee had a heritability of 0.41 while preference for tea had a heritability of 0.36 (Teucher et al. 2007). A Dutch twin study of coffee preference over tea was shown to have a heritability of 0.62 (Vink et al. 2009). One reason for preference for coffee in an individual may be due to taste preference. Caffeine itself can taste bitter to certain individuals. Taste preference testing in Australian adolescent and young adult twins showed that perceived bitterness of caffeine had a broad range heritability of 0.30 after adjusting for age, gender, and other covariates (Hansen et al. 2006). However, this bitterness can be masked by preparation methods, such as adding sugar.

These studies highlight one of the limitations in using dietary intake to estimate individual preference for caffeine in a population study, which is that factors such as individual taste preference and social settings can influence intake, and there may be a need to account for coffee and tea separately when studying caffeine intake. Other limitations include reliance on participant returns of surveys, using self-report of caffeine use and caffeine-related symptoms, imprecise methods of estimating dietary caffeine intake, and cooperation bias from subjects. In addition, results from these studies depend on subject population selected. Whereas most of the studies used general community for sample population, the two studies by Swan et al. used male World War II veterans, which may have certain characteristics different from the general population. Many of these studies are also restricted to Caucasian subjects or conducted in Caucasian-predominant populations, making the result difficult to generalize to other populations.

In summary, the above studies estimate heritability for caffeine-related effects and consumption to range from 0.34 to 0.58, with the heritability for heavy caffeine consumption conspicuously higher at 0.77. A few conclusions can be drawn. First, heavy consumers seem to differ from moderate and light-caffeine users on several accounts. Heavier caffeine users appear to be more influenced by genetics than lighter caffeine users. This is supported by the study by Kendler and Prescott (1999) and by the two studies by Swan et al. (1996, 1997), who reported that genetic variance accounted for 0.36 in overall coffee consumption but 0.51 for heavy consumption. Second, heavy use of caffeine appears to correlate more closely to use of other substances. Multivariate modeling to estimate covariance between tobacco, alcohol, and coffee use calculated the common factor heritability to be 0.41 for heavy users versus 0.28 in all users (Swan et al. 1996, 1997). Third, although patterns of coffee and tea consumption differ in ways beyond the differences in caffeine content, some studies have equated caffeine intake to coffee intake. This may introduce confounds because tea drinking is more common in certain populations.

Taken together, the twin studies show that genetics plays a significant role in individual level of caffeine consumption. Twin studies, while providing valuable insight on the interplay between environment and genetic influence on consumption, do not provide information on the molecular or physiological mechanisms at work. Genetic association studies have been used to identify specific genes that are responsible for the heritable components of these caffeine-related traits. We will briefly review the metabolism and clinical pharmacology of caffeine as a means of introducing the genes that have been examined in association studies.

Basic pharmacology

Caffeine and its metabolites belong to the methylxanthine class, which are structurally similar to cyclic nucleotides, and interact with cyclic nucleotide phosphodiesterases (Arnaud 1987; Daly and Fredholm 1998; Fredholm et al. 1999). Caffeine is absorbed rapidly and completely from the gastrointestinal tract (Arnaud 1987). It is metabolized by cytochrome P-450 enzymes, which represent the rate-limiting step for plasma clearance, and its elimination follows first-order kinetics. P-450 1A2, which is coded for by the gene *CYP1A2*, is the primary isoenzyme responsible for the demethylation of caffeine into dimethylxanthine metabolites paraxanthine, theobromine, and theophylline (Lelo et al. 1986; Miners and Birkett 1996). Each of these metabolites is subjected to further demethylation into monomethylxanthines (Miners and Birkett 1996). Variation in the *CYP1A2* activity, both within and between individuals, represents a major source of variability in pharmacokinetics of caffeine. The clearance of caffeine can vary to up to 40-fold within and between individuals (Kalow and Tang 1991; Kashuba et al. 1998). Notable exogenous factors that affect clearance include numerous drugs,

medications, and smoking status (Grosso and Bracken 2005), as well as caffeine itself (Berthou et al. 1995). Endogenous factors include pregnancy, ethnicity, and genetics. Asian and African populations, for instance, appear to metabolize caffeine at slower rate than Caucasians (Gunes and Dahl 2008).

Under physiological conditions, the main effects of caffeine are due to competitive inhibition of adenosine receptors, mainly A_1 and A_{2A} receptors (Daly et al. 1983). Adenosine receptors are G-protein-coupled receptors located ubiquitously throughout the body. Of the four receptors that have been identified (A_1, A_{2A}, A_{2B}, and A_3), the A_1 and A_{2A} receptors are especially prominent in the central nervous system and are the primary targets of caffeine. Activation of the G_i- or G_o-coupled A_1 causes inhibition of adenyl cyclase and Ca^{2+} channels, whereas activation of G_s-coupled A_{2A} causes activation of adenyl cyclase and voltage-sensitive Ca^{2+} channels (Fredholm et al. 1999). Thus, A_1 and A_{2A} receptors possess partially opposing actions.

A_1 receptors are widely distributed throughout the central nervous system. They are located on presynaptic terminals and mediate inhibitory effects of adenosine on the release of other neurotransmitters, including glutamate (Marchi et al. 2002), acetylcholine (Kurokawa et al. 1996), and dopamine (Yabuuchi et al. 2006). Caffeine administration enhances acetylcholine release through its effects on A_1 receptors (Carter et al. 1995). A_1 receptor blockade enhances the motor effects of D_1 agonists (Fisone et al. 2004; Fredholm et al. 1999). Accordingly, caffeine is thought to produce its stimulatory and arousal effects by releasing this tonic inhibition of dopamine (Dunwiddie and Masino 2001). Chronic treatment with caffeine results in upregulation of adenosine A_1 receptors in the CNS, which persists for 15–30 days after termination of caffeine administration (Boulenger et al. 1983; Marangos et al. 1984). Animal studies show that chronic administration of caffeine produces multiple biochemical changes, including increased densities of A_1 receptors, muscarinic and nicotinic receptors, and increased benzodiazepine receptors associated with $GABA_A$ in the brain (Shi et al. 1993). This upregulation is thought to be responsible for the tolerance to the drug's effects.

The A_{2A} receptors, on the other hand, are located primarily in regions rich in dopaminergic neurons, such as the striatum (Martinez-Mir et al. 1991). The receptors are located postsynaptically on medium-sized spiny neurons in the striatum, which serves as the receiving unit of the basal ganglia (Fink et al. 1992). The basal ganglia controls voluntary movement and motor behavior by relaying input between the cortex and the thalamus. A_{2A} receptors colocalize postsynaptically with D_2 receptors in the medium spiny neurons, and A_{2A} blockade potentiates D_2 receptor-mediated responses. The psychomotor stimulant effects of caffeine are due to antagonism of adenosine's inhibitory actions on the striatal D_2 transmission (Ferre 2008).

Recent research suggests adenosine acts mainly to fine-tune other synaptic transmission in the CNS. For instance, A_1–A_{2A} heteromers modulate glutamergic neurotransmission (Ciruela et al. 2006), whereas A_{2A} receptors have been shown to affect GABAnergic and cholinergic transmission (Kirk and Richardson 1994). Thus, in addition to variations in the A_1 and A_{2A} receptor genes and genes involved in the P450 enzymes, genetic variations in a number of other neurotransmitter functions could influence responses to caffeine.

Genetic variations in caffeine metabolism

Cytochrome P-450

Since caffeine metabolism is mainly determined by the cytochrome enzyme P-450 1A2, genetic variations in this enzyme represent a major endogenous determinant of enzyme activity. Early evidence for genetic variability on *CYP1A2* was first noted when a familial defect in *O*-deethylation, a marker reaction for *CYP1A2*, was reported more than four decades ago (Devonshire et al. 1983; Shahidi 1967). More recently, it has been shown that monozygotic twins share closer kinetic profile than dizygotic twins for caffeine metabolism, with an estimated heritability of 0.725 (Rasmussen et al. 2002). More than 150 SNPs have been identified for *CYP1A2* (dbSNP database: http://www.ncbi.nlm.nih.gov/SNP/), and studies conducted in different ethnic populations have shown large variations in minor allele distributions and common haplotypes frequencies across different groups (Gunes and Dahl 2008).

A single nucleotide C➔A polymorphism at position 734 within intron 1 (rs762551) is correlated with high inducibility of the P-450 1A2 enzyme in Caucasian subjects (Sachse et al. 1999). Smoking subjects with A/A genotype metabolize caffeine at 1.6 times the rate of the other genotypes, while no significant differences are found for nonsmoking subjects. The genetic polymorphism therefore modifies environmental impact on enzyme activity.

How does this allele influence caffeine response or consumption? One study in Costa Rican subjects examined whether the rs762551 single nucleotide polymorphism (SNP) was associated with coffee consumption but failed to detect significant differences between the AA, AC, and CC genotypes (Cornelis et al. 2007). The study finding suggested that rs762551 does not appear to be a major factor in determining individuals' level of caffeine consumption. However, variations in *CYP1A2* activity affect caffeine response in other ways. As discussed below, there is

evidence that *CYP1A2* genotype modifies risk of certain diseases associated with caffeine consumption (discussed under "Genetics and long-term effects of caffeine" section).

Genetic variations in target receptors

Adenosine receptors

Recent genetic studies in animals and humans have implicated polymorphisms in adenosine A_1 and A_{2A} receptors in caffeine response. Animal studies show that A_{2A} receptors are involved in reinforcing behavioral effects of caffeine and are also involved in mediating caffeine's effect on the sleep cycle. More recently, human studies have shown that different A_{2A} receptor polymorphisms are associated with caffeine-induced anxiety and sleep changes in caffeine-sensitive subjects.

The adenosine A_{2A} receptor plays a role in the effects of caffeine on arousal. Mice lacking functional A_{2A} receptors do not show increased wakefulness in response to caffeine administration, indicating that the A_{2A} receptor mediates the arousal response (Huang et al. 2005). In human subjects, the rs5751876 polymorphism in the A_{2A} receptor is associated with sleep impairment and increased electroencephalogram (EEG) beta band activity after caffeine administration (Retey et al. 2007). The *ADORA2A* rs5751876 C/C (1976 C➔T, previously known as 1083 C➔T) genotype was found at greater prevalence in subjects who rated themselves as caffeine sensitive, whereas a higher proportion of T/T genotype was found in self-reported insensitive subjects. Moreover, subjects who self-reported as caffeine sensitive also reported a greater rate of caffeine-induced sleep impairment. Relationship between caffeine sensitivity and sleep disturbance was collaborated by EEG finding of increased beta activity during non-REM sleep in C/C subjects, a pattern typically seen in insomnia patients (Merica 1998; Perlis et al. 2001). In contrast, subjects with C/T genotype showed half the increase in beta activity as compared to C/C genotype, and no change was detected in T/T genotype. Therefore, genotype at rs5751876 influenced risk of caffeine-induced insomnia. This correlation was independent of anxiety, although anxiety was reported with greater prevalence by caffeine-sensitive individuals. While anxiety can itself be a factor in insomnia, it was not correlated with *ADORA2A* genotype in the study.

Studies in human subjects suggest that polymorphisms in the A_{2A} receptor may be responsible for the negative response to caffeine in certain individuals. The *ADORA2A* SNPs rs5751876 and rs35320474 (2592 T/−) have been associated with anxiety in subjects who are light-caffeine users. Individuals with rs5751876 T/T and those with rs35320474 T/T allele reported greater anxiety after acute caffeine administration than other groups (Alsene et al. 2003). A subsequent study using light-caffeine users confirmed this earlier positive association, though this association was no longer significant when analysis was restricted to Caucasian subjects (Childs et al. 2008). The study also found two other SNPs in *ADORA2A* (rs2298383 and rs4822492) to be associated with caffeine-induced anxiety. Interestingly, therefore, two different alleles on the same site, rs5751876, have been associated with two different effects of caffeine—the C allele to caffeine-induced sleep disturbance (Retey et al. 2007) and the T allele to anxiety in Caucasian subjects (Alsene et al. 2003).

The associations between caffeine-induced anxiety and *ADORA2A* polymorphisms are especially intriguing when viewed in context of other studies linking *ADORA2A* to drug-induced anxiety and anxiety disorders. Both rs5751876 C/T and rs35320474 T/− polymorphisms have been associated with increased anxiety after acute administration of amphetamine in healthy subjects (Hohoff et al. 2005). The rs5751876 T/T allele has been associated with panic disorder in Caucasian populations (Deckert et al. 1998; Hamilton et al. 2004), although this association was not replicated in studies in Japanese (Yamada et al. 2001) and Chinese subjects (Lam et al. 2005). It is possible, then, that these genotypes play a role not just in caffeine-induced anxiety but also in anxiety and anxiety disorders overall in certain populations. The finding that the same SNP is associated with both caffeine-induced anxiety and panic disorder supports the observation that panic disorder patients are particularly susceptible to caffeine-induced anxiety (Nardi et al. 2009) and suggests that polymorphisms in the A_{2A} receptor may influence both.

A_{2A} receptors are also involved in the rewarding properties of caffeine. A_{2A} knockout mice self-administer less caffeine than wild-type animals (El Yacoubi et al. 2005), suggesting a role for A_{2A} receptors in the reinforcing properties of caffeine. A cross-sectional study examining the relationship between *ADORA2A* polymorphism and caffeine consumption supports the idea that A_{2A} receptors may also be important for the negative reinforcement properties of caffeine in humans. A study in Costa Rican subjects without history of hypertension found that subjects with rs5751876 T/T were likely to consume less caffeine than C/C subjects (Cornelis et al. 2007). However, the study did not screen the subjects for anxiety, which can itself affect consumption level and has also been linked to rs5751876 T/T as described above. That anxiety can be a factor in caffeine consumption is supported by epidemiological studies, which have shown panic disorder patients consuming less caffeine than subjects without a history of panic disorder (Arias Horcajadas et al. 2005; Lee et al. 1988).

Dopamine receptors

Caffeine administration in animal and human subjects produces effects, such as increased motor activity and self-administration, similar to those of dopaminergically mediated stimulants (Cauli and Morelli 2005; Garrett and Griffiths 1997). Interactions between adenosine and dopamine receptors play a key role in dopamine-potentiating effects of caffeine. Dopamine D_2 and adenosine A_{2A} receptors colocalize in the dorsal and ventral striatal neurons and form a heteromeric complex and exert antagonist effects on each other via G-proteins (Fuxe et al. 2003). Dopamine is an important mediator of the locomotor stimulant effects of caffeine (Zahniser et al. 2000), and when given acutely, caffeine can potentiate locomotor effects of dopamine-releasing agents (Kuribara 1994). The dopamine system is implicated in the rewarding effects of cocaine and opioids, as well as natural rewards such as food and sex (Noble 2000). In animals, chronic caffeine administration enhances amphetamine and cocaine motor stimulant effects, as well as discriminative effects of nicotine, suggesting long-term modification of dopamine receptors (Cauli and Morelli 2005). Long-term administration of caffeine induces changes in tolerance or sensitization of dopamine-mediated responses in rats (Fenu et al. 2000). Therefore, while caffeine does not bind directly to dopamine receptors, it is able to modulate dopaminergic transmission indirectly via its action on the adenosine receptor.

Few studies have directly examined the effect of dopamine polymorphisms on caffeine response in human subjects. Childs et al. (2008) found that a polymorphism in *DRD2* (rs1110976) was associated with caffeine-induced anxiety in the Caucasian subjects. An interaction was reported between *ADORA2A* rs5751876 and *DRD2* rs1079597 that was associated with higher anxiety than either polymorphism alone. The gene–gene interaction is consistent with the animal models showing caffeine interacting with dopamine signaling via adenosine receptor.

The full extent of interaction between adenosine and dopamine receptors in caffeine response has not been fully elucidated. Caffeine has neuroprotective effects on dopaminergic neurons via its interaction with A_{2A} receptor, which may underlie the epidemiological finding that caffeine consumption is inversely correlated with Parkinson's disease, as discussed below.

Genetics and long-term effects of caffeine

Polymorphisms that alter acute response to caffeine may also affect long-term adaptations to caffeine use. While the role of acute caffeine response has been extensively studied, the effects of chronic consumption are less clear. Several properties of caffeine, such as its role in neuroprotection, likely result from adaptive changes due to long-term use rather than from acute exposure. In this section, we will examine the effects of chronic caffeine consumption on Parkinson's and coronary heart diseases, two areas that have received significant attention and in which genetic studies in humans have been conducted.

Case-control studies have noted an inverse correlation between coffee drinking and Parkinson's disease (Ascherio et al. 2001; Ross et al. 2000), though this result has not always been replicated (Checkoway et al. 2002). The relationship appears to be dose dependent, with the correlation strongest in heavy consumers. Studies in mice showed that physiological doses of caffeine were able to attenuate MPTP-induced dopaminergic toxicity (Chen et al. 2001). These properties were mimicked by A_{2A} antagonists but not A_1 antagonists, suggesting that neuroprotection occurs via action at A_{2A} receptor site. Similarly, A_{2A} receptor knockout mice showed reduced MPTP-induced injury as compared to wild-type mice. The exact mechanism of how A_{2A} receptor antagonism can provide dopamine neuron protection remains unclear, but animal studies have shown that A_{2A} receptor blockade protects against ischemia neuronal injuries (Monopoli et al. 1998).

Two studies have examined the association between A_{2A} polymorphisms and incidence of Parkinson's. One study in Singaporean subjects found lower tea and coffee consumption in patients with Parkinson's but did not detect differences in frequency of A_{2A} rs35320474 (2592 T/−) polymorphism between subjects with Parkinson's and controls (Tan et al. 2006). Another case-control study examined rs5751876 and rs3032740 in *ADORA2A* and rs35694136 and rs762551 in *CYP1A2* and did not find any association between coffee drinking and risk of Parkinson's altogether, with or without accounting for genotype (Facheris et al. 2008). While caffeine may offer protection against Parkinson's via A_{2A} receptor, the lack of association between Parkinson's and variants identified with differential caffeine response suggests that neuroprotection may occur via a different mechanism from those of the acute responses.

The role of caffeine in cardiovascular disease has also been extensively studied. Acute ingestion of caffeine or coffee, but not decaffeinated coffee, invokes a rise in systolic and diastolic blood pressure, increases in catecholamine release, and vasodilatation (Papamichael et al. 2005; Smits et al. 1985). However, effects of chronic caffeine consumption in habitualized drinkers are quite different. Some epidemiological studies find that regular coffee intake slightly increases blood pressure (Jee et al. 1999; Noordzij et al. 2005), while others find no difference. Whether caffeine is implicated in cardiovascular diseases is still being debated (Kawachi et al. 1994; Riksen et al. 2009; Sofi et al. 2007). Despite its deleterious effects in acute

settings, several large-scale studies have found that habitual heavy use is protective against cardiovascular disease (Andersen et al. 2006).

One possible factor for the contradictory findings was that different individuals have different risks, and genetics can modulate the risk of developing cardiovascular disease from caffeine consumption. One study found that intake of caffeinated coffee was associated with increased risk of nonfatal myocardial infarction in individuals homozygous for the slow allele *CYP1A2*1F*, marked by A➔C substitution at position 734 (Cornelis et al. 2006). In another prospective study, the risk of acute myocardial infarction in heavy coffee drinkers was found to be higher in subjects possessing allele for lower catechol-*O*-methyl transferase (COMT) activity (Happonen et al. 2006). COMT is the main enzyme responsible for metabolism of catecholamines, which characterize body's response to physiological and psychological stress and have been shown to damage myocardial cells at high concentrations (Abraham et al. 2009). Caffeine may represent a chemical stress to the body due to its ability to potentiate catecholamine release (Lane et al. 1990). The finding of lower COMT activity with higher risk of myocardial infarction points to involvement of circulating catecholamines in caffeine's effect on cardiovascular system, with the implication that slow-metabolizing individuals could be at increased risk due to decreased ability to handle the stress associated with caffeine-induced catecholamine response. A summary of the results of polymorphisms associated with caffeine effects is provided in Table 2.

Conclusion

Genetic diversity can influence a response to caffeine and consumption pattern in many ways. It can confer vulnerability to drug use, such as by modulating vulnerability to rewarding effects via the dopaminergic system. Diversity can also directly alter response such that the individual experiences caffeine more positively or negatively. Data from twin studies show that genetic predisposition toward caffeine use acts mostly via a caffeine-specific mechanism. Current research has implicated the primary enzyme in caffeine metabolism, cytochrome P-450, and caffeine's main target receptors A_1R and $A_{2A}R$ in variability in caffeine response. Laboratory studies in human subjects show that susceptibility of some individuals to certain effects such as anxiety and insomnia can be accounted for by specific alleles of the receptors. Case-control studies in habitual caffeine consumers show that genetics can modify

Table 2 Polymorphisms linked to acute and chronic response to caffeine

SNP	Position	Acute effects	Long-term effects
CYP1A2			
rs762551	Intron I pos. 734: C ➔ A	Increased activity in smokers with A/A genotype (Sachse et al. 1999)	Caffeine consumption does not appear to differ between the genotypes (Cornelis et al. 2007) Risk of nonfatal myocardial infarction higher for subjects with C/C genotype (Cornelis et al. 2006) No association found for risk of Parkinson's disease (Facheris et al. 2008)
rs35694136			No association found for risk of Parkinson's disease (Facheris et al. 2008)
ADORA2A			
rs5751876	1976 C/T	C/C genotype associated with greater caffeine sensitivity, sleep impairment, and increased beta activity during non-REM sleep (Retey et al. 2007) T/T genotype associated with greater anxiety after caffeine (Alsene et al. 2003; Childs et al. 2008)	
rs35320474	2592 T/–	T/T genotype associated with greater anxiety after caffeine (Childs et al. 2008)	No association found for Parkinson's disease or caffeine consumption (Tan et al. 2006)
rs3032740			No association found for risk of Parkinson's disease (Facheris et al. 2008)
DRD2			
rs1110976		Associated with greater levels of caffeine-induced anxiety (Childs et al. 2008)	
COMT			
rs4680	Nucleotide codon 158: Val/Met	Higher risk of acute myocardial infarction in alleles coding for low activity (Met/Met) (Happonen et al. 2006)	

risks to certain health outcomes associated with chronic caffeine consumption.

Future perspective

The widespread use of caffeine makes it an important target in understanding human health and disease. Progress has been made in understanding variability in caffeine responses related to the metabolic enzyme P-450, adenosine receptors A_1 and A_{2A}, and to a more limited extent, dopamine. Further research is likely to identify other sources of variation related to the metabolic enzymes, adenosine receptors, and interactions with dopamine, $GABA_A$, and muscarinic and nicotinic receptors.

One area that has received little attention is genotype effects in different populations. Due to concerns about subject population and/or population stratification, most of the research has been limited to single ethnicities. However, wide ethnic variations are found for *CYP1A2* polymorphisms, and there appear to be variations in the association between *ADORA2A* SNP rs5751876 and caffeine-induced anxiety in different ethnic groups (Lam et al. 2005; Yamada et al. 2001). More studies in non-Caucasian ethnicities are needed to complete our understanding of genotype effects in responses to caffeine.

One of the most exciting directions coming out of caffeine research may be identifying new targets in studying pathogenesis of neurodegenerative disorders. The linkage of adenosine receptor to Parkinson's disease has led to stage III clinical trial testing the adenosine A_{2A} antagonist istradefylline (KW6002) as a new therapeutic option (LeWitt et al. 2008). The same *ADORA2A* SNP that has been found to be related to caffeine-induced anxiety has also been associated with age of onset for Huntington's disease (Dhaenens et al. 2009). It is still unclear why there would be a relationship between A_{2A} receptor and onset for Huntington's disease; however, several recent studies have supported the hypothesis that A_{2A} receptors play a role in neuronal development in Huntington's disease (Popoli et al. 2008). One future direction would be to examine whether caffeine has protective effects against other forms of neurological disorders and dementia.

Finally, knowledge from studying caffeine can be used to explore other drugs. Theophylline, a similarly structured methylxanthine and a minor metabolite of caffeine are used to treat asthma, especially in the pediatric population. However, its use is complicated by narrow therapeutic window and potential toxicity. Like caffeine, theophylline clearance is mainly determined by P-450 activity (Obase et al. 2003). Studying the genetic polymorphisms affecting theophylline response could provide a better means to select appropriate doses.

From these studies, it is clear that studying the genetic basis for caffeine response not only enhances our understanding of the mechanism of action for caffeine itself but also to the biochemical function of the receptors and their associated neurotransmitters. In addition, these studies have also led to new fields in biomedical research: how genetics influences response to drugs and sheds new light on pathophysiology of commonly studied diseases. Further research is needed to understand the functional significance of these genotypes and the interaction between the drug, environment, and biological system.

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