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LETTER TO THE EDITORS

More on *ADORA*

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Letter to the editors of *Psychopharmacology*:

We recently published a review on genetic factors influencing responses to caffeine and consumption of caffeine (Yang et al. 2010). Unfortunately, our review went to press just before an important additional paper was published on this topic (Rogers et al. 2010). Here, we attempt to integrate the new findings from Rogers et al. with the conclusions of our review.

The recently published study by Rogers et al. (2010) investigated whether single nucleotide polymorphisms (SNPs) associated with caffeine-induced anxiety might also affect habitual caffeine intake and whether habitual intake moderates the anxiogenic effect of caffeine. The experiment examined associations between SNPs in two adenosine receptors (*ADORA2A* and *ADORA1*) and caffeine-induced anxiety in non-consumers/light consumers and medium/heavy consumers of caffeine. Consistent with previous reports (Alsene et al. 2003; Childs et al. 2008), the researchers found an association between the T/T genotype of rs5751876 (p=0.002) and caffeine-induced anxiety. Similar results were found for rs3761422 (p=0.004), which is in strong linkage disequilibrium with rs5751876. There were no associations with other SNPs in the eight *ADORA2A* loci (α=0.00625, adjusted for multiple testing) or the seven *ADORA1* loci (α=0.00714) tested. However, this effect was moderated by habitual consumption. All non-consumers/light consumers exhibited significant increases in anxiety after caffeine while medium/heavy consumers did not, regardless of genotype. Contrary to their hypothesis, total caffeine consumption did not differ among different genotypes. Thus, it appears that while rs5751876 is associated with anxiety after caffeine, this effect may be moderated by habitual consumption such that regular consumers develop tolerance to the anxiogenic effects of caffeine. The authors conclude that susceptibility to caffeine-induced anxiety does not appear to influence levels of habitual caffeine intake.

These findings corroborate some previous findings (Childs et al. 2008, Alsene et al. 2003), but are inconsistent with another study (Cornelis et al. 2007). The association between rs5751876 T/T genotype and caffeine-induced anxiety is consistent with reports by Childs et al. (2008) and Alsene et al. (2003); however, the lack of association between this genotype and caffeine consumption is not consistent with findings reported by Cornelis et al. (2007), who found that rs5751876 T/T individuals, particularly smokers, consumed less caffeine. The two studies were conducted in very different populations: the Rogers study recruited healthy Caucasian Europeans with mean age of 30–35 years, whereas the Cornelis study tested Costa Rican survivors of myocardial infarction with mean age of 56–57 years. Therefore, other factors such as age and survival differences may have contributed to the observed effects of *ADORA2A* genotype on caffeine consumption.

The finding that frequent consumers of caffeine report less anxiety than lighter consumer, regardless of genotype, can be explained by several factors. First, in heavy caffeine consumers, the potential anxiogenic effects of acute doses of the drug may be masked by presence of, and relief from, caffeine

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withdrawal. Second, certain users may continue to consume caffeine despite the initial anxiogenic effects because of other positive aspects of caffeine or environmental influences, and with regular use, develop tolerance to its anxiogenic effects. Third, certain individuals may not experience same degree of anxiety because of other genetic and environmental factors.

Taken together, these studies illustrate the interplay of genes and environment in drug effects. By comparing drug effects in users with different genotypes and with different consumption patterns, Rogers et al. sought to assess how behavior and environment interact with genetic predisposition to result in certain outcomes. As discussed in our review and highlighted here, physiologic adaptation plays an important role when studying genetic effects on drug response. While the study focused on anxiogenic effects of caffeine, other consequences of caffeine use, such as blood pressure changes, and cognitive effects may also be modulated through adaptation. Apparent discrepancies across studies also illustrate the complexities of genetic research, with co-varying factors such as age, race, environmental factors, and population selection, all impacting study findings. Further interesting studies on this topic are likely to be forthcoming, in view of the growing scientific and clinical interest in adenosine, pharmacogenetics, and mechanisms of stimulants such as caffeine.

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