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Title: Letter to the Editor – Caffeine, CYP1A2 genotype, and sports performance; is timing important?

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To The Editor

I read with great interest the recent papers authored by Rahimi [1], published in this journal, and by Guest and colleagues [2], published in *Medicine & Science in Sport & Exercise*, exploring the ergogenic effects of caffeine on different *CYP1A2* genotypes. Briefly, Rahimi reported 6mg/kg of caffeine did not enhance resistance exercise performance in C allele carriers in a cohort of males, but did for AA genotypes. Similarly, Guest et al. [2] found that caffeine was ergolytic for endurance performance at a dose of 4mg/kg for CC genotypes, was ergogenic at doses of both 2- and 4mg/kg for AA genotypes, and neutral for AC genotypes at both doses, as well as for CC genotypes at 2mg/kg. Since 2012, a number of papers have been published exploring the impact of this particular polymorphism on caffeine's performance benefits, with equivocal results [3,4]. These previous studies tended to be hindered by complex study designs [4], or low subject numbers [3]. The latter point is particularly important, given that the frequency of CC genotypes tends to be very low (~8%) [2], illustrated by the complete absence of CC genotypes available for group analysis in Rahimi's cohort [1]. As such, the additional insights garnered from both Rahimi [1] and Guest and colleagues [2] shed further insight into the inter-individual variation of ergogenic effects following caffeine ingestion.

The results, however, promote significant cognitive dissonance. As an AC genotype who used caffeine extensively as an ergogenic aid during my professional athletic career, do I really believe that caffeine had no performance benefits for me? It's hard for me to reach such a conclusion, even though the results of both Rahimi and Guest and colleagues' research [1,2] suggest as much. I'm sure many other practitioners feel the same, and indeed perhaps worry that the standard caffeine recommendations are harmful, or at best neutral, for a significant proportion of the athletes they work with [5].

The mechanism proposed by Guest et al. [2] is that, because C allele carriers metabolise caffeine at a slower rate than AA genotypes [6], they experience prolonged vasoconstriction, which is likely to be performance limiting in endurance events where the transfer of oxygen and nutrients to the working muscle is crucial. Additionally, Womack and colleagues [3] speculated that the metabolites of caffeine – paraxanthine, theobromine, and theophylline – have additional ergogenic effects; in this case, the presence of these ergogenic substances would be lower in C allele carriers at a given time point due to the slower metabolization of caffeine, reducing caffeine's performance benefits. This proposed mechanism was echoed by Rahimi [1].

If the above mechanisms are indeed correct, then there remains the possibility that caffeine can still be ergogenic for C allele carriers, but that such individuals need to consume it a greater amount of time prior to exercise. In the majority of studies – including Guest et al. [2] and Rahimi [1] – subjects consume caffeine ~60 minutes pre-exercise. However, for C allele carriers, could the ergogenic effects of caffeine be restored by utilizing a caffeine dose 90 or 120 minutes pre-exercise? Such an hypothesis is, of course, speculative, and requires testing – but it does represent a potential way by which caffeine can indeed be ergogenic for all. The resolution of whether caffeine is truly ergolytic or neutral for *CYP1A2* C allele carriers, or if it merely necessitates a different caffeine strategy, represents an important step on the journey towards more personalized sports nutrition guidelines.

Compliance with Ethical Standards:

Conflict of Interest: Craig Pickering is an employee of DNAFit Ltd, a genetic testing company. He received no financial incentives for the preparation of this manuscript, and the views contained within are his, and not representative of DNAFit Ltd.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

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