"**Pharmacogenomics of Inhaled Beta2-agonists and Athletic Performance**"

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Project review

Beta2-agonists are a type of medication that is commonly used in the treatment of asthma. They can have other actions other than treating asthma that may have the potential to improve exercise performance.

In the past 25 years, there has been a trend for an increase in applications for permission to use 2-agonists from athletes competing in Olympic Games. In fact athletes that use these agents win a disproportionately high number of medals. Previous research has looked at unselected groups, and found no doping benefit from these agents. Recent research has shown that there is a large variety in the genes that affect how individuals respond to these 2-agonists. We will look at variations in the genetic response to these medications. Specifically we will divide athletes into those with a genetically high response to these drugs and those with a lower response. We will then compare their exercise performance following the administration of a 2-agonist. We hypothesize that a subgroup of athletes with certain genetic variations will benefit from 2-agonists while the rest will not. If some athletes are achieving enhanced performance from asthma medication, then the rules surrounding their use in sport will need to be reviewed.

Results and Conclusions

The aims of this project were (1) to determine if the A46G single-nucleotide polymorphism (SNP) and the C79G SNP of the adrenergic β2-receptor gene (ADRB2) and the A663T SNP of the sodium channel gene (SCNN1A) affect time-trial cycling performance after the inhalation of salbutamol in male cyclists with and without exercise-induced bronchoconstriction (EIB); (2) to assess if women experience a greater increase in lung function following the inhalation of β2-agonists compared to men and therefore increase their 10-km cycling time-trial performance; and lastly, (3) to investigate if there is an ergogenic effect to the inhalation of 1600 μg of salbutamol, a supratherapeutic dose, in male cyclists with and without EIB.

In total, 130 competitive female and male athletes, aged between 19 and 45 years were screened (103 males, 27 females). Athletes performed two simulated 10-km time-trials on a cycle ergometer following inhalation of either 400 µg (studies I and II) or 1600 µg (study III) of salbutamol or placebo. Change in forced expiratory volume in 1 second (FEV1) was assessed immediately before and following inhalation. Performance was measured by mean power output over the time-trial duration.

Percent change in FEV1 following the inhalation of salbutamol was significantly increased compared to placebo ($p < 0.001$) in all three studies, regardless of athletes' susceptibility to EIB. Despite this increase in lung function following salbutamol use, time-trial performance was not improved. Genetic variation at the ADRB2 and SCNN1A genes did not affect the bronchodilatory response and time-trial performance to inhaled salbutamol in male and female athletes with and without EIB. Furthermore, there was no difference in the percent change in FEV1 following the inhalation of 400 µg of salbutamol between male and female cyclists. However, there was a decrease in mean power output during the salbutamol time-trial of 3 Watts compared to the placebo time-trial in female athletes, but not in male athletes. This could have been caused by an increased salbutamol dosage-to-weight ratio in women compared to men. Lastly, a supra-therapeutic dose of salbutamol did not affect 10-km time-trial performance in male cyclists, but lead to significant increases in heart rate and minute ventilation, common side-effects of IBAs, in athletes without exercise-induced bronchoconstriction.

In conclusion, despite a significant improvement in lung function following the inhalation of salbutamol, 10-km time trial performance was not improved, regardless of asthma status, genetic variation at the ADRB2 and SCNN1A genes, sex and salbutamol dose.