PROJECT REVIEW

"AICAR Determination of endogenous values to establish a threshold to distinguish exogenous administration"

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The influence of orally available drugs on the productivity of selected genes has been demonstrated manifold in the past, and an endogenous substance termed AICAR has been found to be of considerable interest in the treatment of the metabolic syndrome associated with type-II diabetes, obesity, etc. The stimulation of fat utilization and the increased production of mitochondria generated considerable concerns whether this substance might be misused in sports also since laboratory rodents demonstrated significantly enhanced endurance performance after a 4-weeks treatment with AICAR, and the World Anti-Doping Agency has banned its use since January 2009. Due to the natural occurrence of AICAR as a (by-)product in purine biosynthesis, a quantitative determination of natural urinary AICAR values in healthy individuals is necessary to provide a means to uncover the illicit administration of this drug, which should increase the renal elimination and, thus, the urine concentration of AICAR, significantly.

Preliminary data have demonstrated that urinary AICAR levels vary considerably depending on the studied population (athletes, healthy individuals, vitamin B12 or folic acid deficient persons, etc.), and AICAR concentrations higher than 7,500 ng/mL were detected in athletes' doping control samples. Since it can not be excluded that some athletes misuse AICAR already today, urinary AICAR levels of healthy individuals shall be determined to obtain reliable reference values. Within the planned project, a cohort of approximately 500 sport students shall be analyzed for urinary AICAR levels including pre- and post-exercise samples, males and females, as well as different sport disciplines (endurance, strength, and game sports) to allow a statistical evaluation of the obtained results and enable the consideration of threshold value(s) that are indicative for AICAR misuse in sports. Future projects might further elucidate the option to differentiate endogenous AICAR from the synthetically derived analog by isotope-ratio mass spectrometry.

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Results and Conclusions

The adenosine monophosphate activated protein kinase (AMPK) activator 5-amino-4-imidazolecarboxyamide ribonucleoside (AICAR) was found to significantly enhance the endurance of rodents even under sedentary conditions. Thus, usage of this substance was classified as gene doping and AICAR was added to the list of prohibited substances of the World Anti-Doping Agency (WADA). Due to the endogenous production of AICAR in healthy humans, considerable amounts are present in the circulation and, thus, are excreted into urine. Considering these facts, the present study was initiated to establish reference values of renally cleared AICAR in elite athletes. Therefore a quantitative analytical method by means of isotope-dilution liquid chromatography coupled to tandem mass spectrometry, following a sample preparation consisting of a gentle dilution of native urine, was developed. Doping control samples of 500 healthy volunteers were analysed and AICAR concentrations in urine were determined. The statistical evaluation showed a significantly better distribution (normality for log-transformed values) for creatinine corrected data compared to density correction. Data evaluation of the analysis of 500 urine samples yielded a mean concentration of 863 ng/mL with sd=462 ng/mL (corrected via density) or 552 ng/mg with sd=290 ng/mg (corrected via creatinine). Computing the 99.99% reference intervals values for the creatinine corrected amounts of 3361 ng/mg were obtained and these calculations for the present dataset suggest that amounts of urinary AICAR higher than 3500 ng/mg are not consistent with an endogenous production in healthy humans.