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Genetic variability and the urinary testosterone/epitestosterone ratio

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Abstract

The urinary testosterone/epitestosterone (T/E) ratio determination, based on quantification of testosterone glucuronide and epitestosterone glucuronide in urine, is a major tool in trying to expose illegal use of exogenous testosterone by sportsmen. As a result of the analysis of authentic urine samples collected from male athletes for whom there was no indication of testosterone abuse, as determined by isotope analyses, we found that the main reason for high T/E results was a low epitestosterone glucuronide concentration rather than a high level of testosterone glucuronide. Metabolic processes that determine the urinary concentration of testosterone and epitestosterone are complex and not fully understood. In particular, little is known how the T/E ratio is affected by genetic variations in genes that encode enzymes and transporters that are involved in the metabolism and secretion of these steroids.

Glucuronidation is the major conjugation pathway of anabolic steroids in humans and changes in the activity or the expression level of the UDP-glucuronosyltransferases (UGTs) that are directly involved in testosterone or epitestosterone glucuronidation could significantly change the T/E ratio. Our recent study was dedicated to close examination of the glucuronidation of T and E by the human UGTs, including possible effects of genetic variability, i.e. polymorphism on the conjugation activity. Further interest in studying testosterone and epitestosterone glucuronidation by individual UGTs is related to the similarity of their chemical structures. Testosterone and epitestosterone are diastereomers that

differ only in the configuration of the hydroxyl that is bound to carbon 17, the same functionality that undergoes conjugation during the glucuronidation reaction.

Glucuronidation assays with the 19 human UDP-glucuronosyltransferases (UGTs) of subfamilies UGT1A, UGT2A, and UGT2B revealed that UGT2B17 is the most active enzyme in testosterone glucuronidation. UGT2B17 does not glucuronidate epitestosterone, but inhibition studies revealed that it binds epitestosterone with affinity similar to that of testosterone. Epitestosterone glucuronidation is catalyzed mainly by UGT2B7, and the Michaelis-Menten constant (K_m) of this reaction is significantly lower than the K_m of UGT2B17 for testosterone. Although UGT2B7 and UGT2B17 exhibited high, although converse, stereoselectivity in testosterone and epitestosterone glucuronidation, UGT2A1, an extrahepatic enzyme that is expressed mainly in the nasal epithelium, catalyzed the glucuronidation of both steroids at considerable rates and similar kinetics. The results shed new light on the substrate specificity and stereoselectivity of human UGTs.

For the complete paper, please, see the following reference:

Sten T, Bichlmaier I, Kuuranne T, Leinonen A, Yli-Kauhaluoma J, Finel M. (2009) UDP-glucuronosyltransferases (UGTs) 2B7 and UGT2B17 display converse specificity in testosterone and epitestosterone glucuronidation, whereas UGT2A1 conjugates both androgens similarly. DMD 37, 417-423.