Project Review

"Genetic variability, the urinary testosterone/epitestosterone ratio and anabolic steroid abuse"
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The urinary testosterone/epitestosterone (T/E) ratio determination, based on quantification of testosterone glucuronide and epitestosterone glucuronide in urine, is a major tool in attempts to expose illegal use of exogenous testosterone by sportsmen. Nonetheless, the metabolic processes that determine the urinary concentration of testosterone and epitestosterone are complex and not fully understood. In particular, little is currently 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. It is important to gain deeper knowledge on the metabolism of both testosterone and epitestosterone since changes in either system would affect the all-important T/E ratio. In addition, it is essential to further develop the doping test methods for the detection of anabolic steroids abuse in order to make them less sensitive to genetic polymorphism among the athletes.

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. A part of the proposed research will therefore be dedicated to close examination of the glucuronidation of anabolic steroids by the human UGTs, including possible effects of genetic variability (polymorphism) on the glucuronidation of testosterone and epitestosterone. The second major section of the proposed research will concentrate on the urinary concentrations of several steroid metabolites in order to provide a better picture of possible abuse of testosterone or its prohormones, even by athletes that carry mutations within their UGTs, or in other proteins that take part in the metabolism and secretion of testosterone and/or epitestosterone. The combined results are expected to provide valuable information that could significantly improve the fight against doping.
Genetic variability, the testosterone/epitestosterone ratio and anabolic steroids abuse

Results and Conclusions

The main conclusions of our studies within this WADA supported project are the following:

1. Examination of all the 19 human UGTs of subfamilies 1A, 2A and 2B revealed that UGT2B17 is by far the main contributor to testosterone glucuronidation in man. This result provides the explanation for the previously observed effect of UGT2B17 deletion on the T/E.

2. Examination of all the 19 human UGTs of subfamilies 1A, 2A and 2B revealed that UGT2B7 is by far the main contributor to epitestosterone glucuronidation in man.

3. Both UGT2B7 and UGT2B17 are the major contributors to the glucuronidation of androsterone as well as etiocholanolone, even if UGT2B17 has significantly higher affinity and higher turnover rate with etiocholanolone.

4. UGT2B7 is the main contributor to the glucuronidation of 5α-diol on the 3-OH, whereas UGT2B15 and UGT2B17 are mainly responsible for its glucuronidation on the 17-OH.

5. UGT2B17 is the main contributor to the glucuronidation of 5β-diol, primarily on the 17-OH.

6. UGT2A1 has the capacity for glucuronidating testosterone, epitestosterone, and etiocholanolone at high rate, but it probably does not contribute noticeably to the level of androgen glucuronides in the urine due to its limited expression.

7. Low levels of urinary testosterone glucuronide concentration are not compensated for by higher level of testosterone sulfate.

8. Low levels of urinary epitestosterone glucuronide, not high levels of testosterone glucuronide, are the main reason for high T/E in athletes that have not used exogenous testosterone.

9. In an effort to develop a system for detecting possible abuse of exogenous testosterone by sportsmen that will not be dependent on the activity of UGT2B17, we suggest to concentrate on 3-glucuronide of 5α-diol. Another possible target molecule from this point of view is androsterone glucuronide.

Publications