

PROJECT REVIEW

“Human androgen disposition decisive determinants of variability”

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Anabolic androgenic steroids (AAS) behave differently in the human body. The human organism deals with these compounds differently in respect of uptake, distribution into different organs, metabolism and excretion. We recently demonstrated that $\frac{3}{4}$ of Oriental people have a severely compromised capacity to excrete testosterone in the urine compared to only 10 % in people from the west. This is a confounder in the doping test program. Moreover, many samples are classified as atypical positive and needs extensive analysis in order to determine if true positive. Most of these atypical findings are negative and therefore it is urgent to find a biomarker that could decrease the costly and time consuming management of these samples.

In the way towards personalised test programmes, Bayesian inference techniques are known to suit particularly well. To further improve the new individualised steroid profile passport, we will conduct several human studies with different routes of administration, preparations, and doses of testosterone in order to assess the sensitivity and specificity of the test program.

Our research program encompasses projects designed to investigate variation in AAS disposition including inter-ethnic and gender differences. We will study both testosterone and synthesized agents with anabolic androgenic effects (nandrolone, stanozolone).

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Result and Conclusion

The overall aim of the project has been to identify and quantitate genetic and other mechanisms of variation in the bioavailability, metabolism, and excretion of androgens (endogenous as well as exogenous). We have also focussed on the serum concentration profiles of testosterone in genetic panels of healthy volunteers. Serum concentrations are relevant comparators to effects of, and adverse reactions to androgens. Therefore, they are highly interesting.

Serum concentrations and bioavailability have been studied and related to bioactivating enzymes and transporters. Variation in these parameters are likely determinants of the effects of androgens and of interest not only for the capacity of doping tests but also for the user profile, risk exposure etc.

- a) Validation of putative biomarkers that could be used to increase the positive and the negative predictive values of testosterone doping (PPV, NPV) was addressed in the following publication: Schulze JJ, Thörngren JO, Garle M, Ekström L, Rane A. “Androgen sulfation in healthy UDP-glucuronosyl transferase 2B17 enzyme-deficient men” *J Clin Endocrinol Metab.* 2011 Nov;96(11):3440-7. Epub 2011 Aug 17.
- b) Other endpoints related to adverse effects of testosterone were also studied in healthy volunteers, e.g. the serum lipid profile. Garevik N, Skogastierna C, Rane A, Ekstrom L. “Single dose testosterone increases total cholesterol levels and induces the expression of HMG CoA Reductase” *Subst Abuse Treat Prev Policy.* 2012 Mar 20;7(1):12. [Epub ahead of print]
- c) The effect of androgen abuse on endocrine pituitary-gonadal axis was studied in Garevik N, Strahm E, Garle M, Lundmark J, Ståhle L, Ekström L, Rane A. “Long term perturbation of endocrine parameters and cholesterol metabolism after discontinued abuse of anabolic androgenic steroids” *J Steroid Biochem Mol Biol.* 2011 Nov;127(3-5):295-300. Epub 2011 Aug 22
- d) We have shown that the main nandrolone metabolite (19 norandrosterone glucuronide) could be detected in urine up to one year in AAS abusers.
- e) The androgen profile in urine in different female populations was studied. It is of great importance that the athlete’s steroid passport program, will be able to correct for and consider all possible variability in longitudinal steroid profiles in women. Ekström L, Gök E, Johansson M, Garle M,

Rane A and Schulze JJ. Doping and Genetic Testing: Sex Difference in UGT2B15 expression, Testosterone Glucuronidation Activity and Urinary Testosterone/Epitestosterone ratio. *Current Pharmacogenomics and Personalized medicine*, 2012, June 10:125-131

- f) We have observed conspicuous inter-individual differences in serum concentrations of testosterone after administration of the same testosterone dose to healthy volunteers. Ekström, L., Schulze, J., Guillemette, C., Belanger, A., Rane A. "Bioavailability of testosterone enanthate dependent on genetic variation in the phosphodiesterase 7B (PDE7B) but not on the UDP-glucuronosyltransferase (UGT2B17) gene" *Pharmacogenetics and genomics* 2011 Jun;21(6):325-32.
- g) Determinants of androgen access to androgen receptors also include transporters, along with metabolising enzymes from various families. We have investigated organic anion transporting polypeptides (OATP). Schulze JJ, Johansson M, Rane A, Ekström L. "Genetic variation in SLCO2B1 is associated with serum levels of testosterone and its metabolites prior to and two days after testosterone administration" *Current Pharmacogenomics and Personalized Medicine* to be published Vol. 10, No. 3, 2012.
- h) In one publication; Sten, T., Finel, M., Ask, B., Rane, A., Ekström, L. "Non-steroidal anti-inflammatory drugs interact with testosterone glucuronidation", *Steroids* 2009 Nov;74(12):971-7, we have studied the inhibitory effect of these NSAIDs on recombinant UGT2B17 and UGT2B15, as well as other human hepatic UGTs that revealed low but detectable testosterone glucuronidation activity, namely UGT1A3, UGT1A4, UGT1A9 and UGT2B7.

Since many of the individuals devoid of the UGT2B17 gene would not reach a T/E ratio of 4.0 after testosterone intake future test programs will most likely shift from the population based- to an individual-based T/E cut-off ratios using Bayesian inference. Schulze, JJ., Lundmark, J., Garle., Ekström, L., Sottas, PE., Rane, A. " Substantial advantage of a combined bayesian and genotyping approach in testosterone doping tests." *Steroids*. 2009 Mar;74(3):365-8