Intratesticular testosterone is increased in men and mouse models with Klinefelter syndrome and may not be released into the circulation due to altered testicular vascularisation

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Introduction

Both, patients with Klinefelter syndrome (47,XXY KS) and the 41,XX^{Y*} mouse model for KS show lowered peripheral serum testosterone levels compared to controls (1). However, Leydig cells are hyperplastic and hyperactive in the KS mouse model and **intratesticular testosterone** (ITT) concentrations are similar to controls. We therefore analysed ITT in biopsies from KS patients and tested the hypothesis that altered testicular vasculature might be the cause of hampered testosterone transfer into the circulation.

Aim

To analyse ITT in biopsies of KS patients and to evaluate whether testicular blood vessels are altered in KS mouse model testis.

Methods

ITT concentrations were measured in biopsies of 11 KS and in 10 vasectomised patients and serum testosterone in blood of 41,XX^{Y*} and control mice (n=5). In the testes of 41,XX^{Y*} and control mice areas covered by blood vessels (Fig. 1) were measured and presented as percentage of the total testicular areas by image processing software.

Results

KS patients showed significantly reduced serum testosterone compared to controls (10.2±6.0 vs. 15.2±3.8 nmol/l) while ITT (per whole testis) was in the same range (132.8±84.0 vs. 152.1±100.7 nmol/testis). Concerning testicular hormones, ITT was the highest in KS when analysed per gram of tissue. Serum testosterone was also reduced in adult XX^{Y*} mice, although significance was not reached.

In XX^{Y*} mice areas covered by blood vessels within the testes were significantly lower (262.8 ± 143.8 µm² vs. 906.9 ± 369.9 µm² in XY*, $p < 0.01$). The ratio of blood vessel area per testes and therefore correcting for the smaller XX^{Y*} testes also revealed a significant reduction in XX^{Y*} (1.5 ± 0.3‰) compared with fertile controls XY* (4.1 ± 1.3‰, $p < 0.01$).

Additionally, the distribution of blood vessel size was different: larger blood vessels covering an area of more than 867µm², which comprised 13% of all vessels and occupied 55% of the total vessel area in XY* mice were lacking in XX^{Y*} males (Fig. 2).

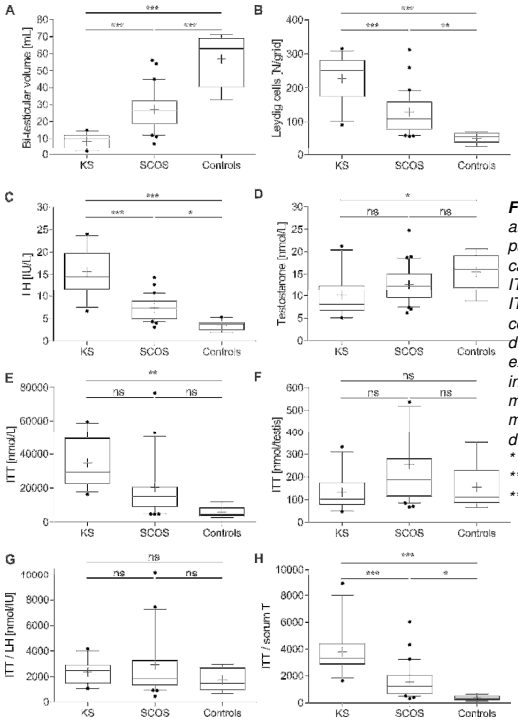

Fig 1: *Selected clinical and testicular parameters (A-F) and calculated ratios of ITT/LH (G) and ITT/serum T (H). Boxes contain 50% of the distribution, whiskers extend to 10-90%; lines in boxes represent the median, crosses the mean. Significant differences marked with * $p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$.*

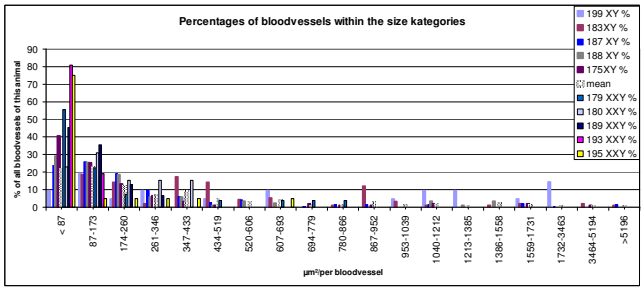

Fig 2: *Percentages and distribution of murine testicular blood vessels along size categories. Individual animals are shown with the XY* and XX^{Y*} kariotype.*

Conclusion

KS patients exhibited low peripheral serum testosterone but normal ITT. However, the ITT was increased in KS when analysed per gram tissue. In conjunction with the different vasculature observed in mice, hampered hormone release from the testis seems a likely explanation for the lower serum testosterone. Whether this is primarily caused by a general disturbance in angiogenesis or is secondary to the architectural changes following postnatal germ cell loss remains to be determined.

References

1. ***Wistuba J*** *2010 Animal models for Klinefelter's syndrome and their relevance for the clinic. Mol Hum Reprod 16:375-385*

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