Göteborg, 2023

Androgens and progesterone in tissues and the gastrointestinal tract

Mapping of tissue-specific sex steroid levels in mice

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Medicinaregatan 3, den 9 november 2023 klockan 13.00

av **Hannah Colldén**

Fakultetsopponent: Dr. Richard Auchus, Professor, University of Michigan Health, USA

Avhandlingen baseras på följande delarbeten

I. Colldén H*, Nilsson ME*, Norlén AK, Landin A, Windahl SH, Wu J, Gustafsson KL, Poutanen M, Ryberg H, Vandenput L*, Ohlsson C*. **Comprehensive sex steroid profiling in multiple tissues reveals novel insights in sex steroid distribution in male mice.** Endocrinology 2022; 163(3):bqac001 *contributed equally

II. Colldén H, Nilsson ME, Norlén AK, Landin A, Windahl SH, Wu J, Horkeby K, Lagerquist MK, Ryberg H, Poutanen M, Vandenput L*, Ohlsson C*. **Dehydroepiandrosterone supplementation results in varying tissue-specific levels of dihydrotestosterone in male mice.** Endocrinology 2022; 163(12):bqac163 *contributed equally

III. Colldén H, Landin A, Wallenius V, Elebring E, Fändriks L, Nilsson ME, Ryberg H, Poutanen M, Sjögren K, Vandenput L, Ohlsson C. **The gut microbiota is a major regulator of androgen metabolism in intestinal contents.** Am J Physiol Endocrinol Metab. 2019; 317(6):E1182-E1192

IV. Colldén H, Hagberg Thulin M, Landin A, Horkeby K, Lagerquist MK Wu J, Nilsson KH, Grahnemo L, Poutanen M, Ryberg H, Vandenput L*, Ohlsson C*. **Dietary progesterone contributes to intratissue levels of progesterone in male mice.** Endocrinology 2023; 164(8):bqad103 *contributed equally

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Hannah Colldén

Avdelningen för internmedicin och klinisk nutrition, Institutionen för medicin, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2023.

Abstract

Sex steroids such as androgens can exert both positive and negative effects in tissues and are important in physiology and pathophysiological states of men and women. Androgens originate mainly from the gonads. Local androgen levels in tissues are also regulated by intracrine processes, resulting in local levels not always being reflected by circulating levels. Mouse models are commonly used to study sex steroid-related disorders, but a lack of sufficiently sensitive and specific methods has prohibited accurate measurement of the low sex steroid levels in mouse tissues. Here, we developed and validated a gas chromatography – tandem mass spectrometry method capable of determining a broad panel of sex steroids in tissues and used it to map local sex steroid levels in tissues of mice in different conditions/treatments. We found that supplementing castrated male mice with dehydroepiandrosterone (DHEA) caused high androgen levels in the prostate and liver, raising concerns about the unsolicited use of DHEA by the public. Also, the gut microbiota was involved in the deconjugation of intestinal androgens, suggesting a possible mechanism for the relationship between androgen-related conditions and the gut microbiota proposed by experimental and epidemiological studies. Finally, progesterone was the most abundant sex steroid in castrated male mice, and the progesterone levels were surprisingly unaffected by both adrenalectomy and castration. We found that dietary progesterone was absorbed into tissues of male mice; therefore, we suggest food as a possible source of progesterone in men, perhaps of relevance for men with prostate cancer.

In conclusion, measurement of local sex steroid levels in tissues is a novel method that could bring new understanding of pathways and mechanisms in androgen-related disorders and contribute to future development of more selective treatments for sex steroid-related diseases.

Keywords: androgens, progesterone, intracrinology, gastrointestinal tract, gut microbiota

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