COMT Genotype, sex steroids and bone phenotype in man and mice

Akademisk avhandling

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av

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Avhandlingen baseras på följande arbeten:

I. Association between the low activity genotype of catechol-O-methyltransferase and myocardial infarction in a hypertensive population.
European Heart Journal 2004 Mar; 25(5):386-91
Eriksson AL, Skrtic S, Niklason A, Hultén LM, Wiklund O, Hedner T, Ohlsson C

II. The COMT val158met polymorphism is associated with peak BMD in men.
Lorentzon M, Eriksson AL, Mellström D, Ohlsson C
Journal of Bone and Mineral Research 2004 Dec; 19(12):2005-11

III. The COMT val158met polymorphism is associated with early pubertal development, height and cortical bone mass in girls.
Eriksson AL, Suuriniemi M, Mahonen A, Cheng S, Ohlsson C
Pediatric Research 2005 Jul; 58(1):71-7

IV. Association between physical activity and BMD in young men is modulated by catechol-O-methyltransferase (COMT) genotype: the GOOD study.
Lorentzon M, Eriksson AL, Nilsson S, Mellström D, Ohlsson C
Journal of Bone and Mineral Research 2007 Aug; 22(8):1165-72

V. The COMT val158met polymorphism is associated with prevalent fractures in Swedish men.
Eriksson AL, Mellström D, Lorentzon M, Orwoll ES, Redlund-Johnell I, Grundberg E, Holmberg A, Ljunggren Ö, Karlsson MK, Ohlsson C
Bone. 2008 Jan; 42(1):107-12

VI. Catechol-*O*-methyltransferase is a physiological regulator of bone growth and cortical bone dimensions in female mice.
Eriksson AL, Forsberg MM, Karayiorgou M, Gogos JA, Männistö PT, Ohlsson C
Manuscript

COMT GENOTYPE, SEX STEROIDS AND BONE PHENOTYPE IN MAN AND MICE

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ABSTRACT

Sex steroids are of profound importance for several physiological processes including reproduction, growth, and maintenance of skeletal integrity. Serum levels of sex steroids are associated with bone mineral density (BMD) and have been shown to be predictive of fracture risk in older people. Sex steroid levels in serum, and also BMD and fracture risk, are under genetic control. Catechol-O-methyltransferase (COMT) is an important estrogen-degrading enzyme. In the COMT gene there is a single nucleotide polymorphism (SNP), COMT val108/158met, differentiating three levels of activity: high ($COMT^{HH}$), intermediate ($COMT^{HL}$), and low ($COMT^{LL}$), as a result of lower enzyme activity of the Met variant.

The aim of the studies in this thesis was to investigate the role of COMT val108/158met for serum levels of sex steroids, skeletal phenotype, and fracture risk. Four human cohorts and one mouse strain devoid of COMT activity (COMT KO) were used.

In girls in early puberty, $COMT^{LL}$ was found to be associated with higher estradiol (E2) levels, increased longitudinal and radial cortical bone growth, and an earlier pubertal development compared with $COMT^{HH}$. Girls with the $COMT^{LL}$ genotype were 5.4 cm taller on average than girls with $COMT^{HH}$. Regression models indicated that most of the associations with pubertal development and growth were mediated through elevated levels of E2. This is plausible, because in theory the $COMT^{LL}$ genotype would be associated with higher E2 levels due to impaired degradation of estrogens. Increased longitudinal and radial cortical bone growth was also seen in COMT KO mice, compared with their wild-type siblings.

In young adult men, COMT genotype was found to be associated with BMD and it was also found to be a modulator of the positive associations previously found in these young adult men between physical activity (PA) and BMD. In general, the association between PA and BMD was stronger in the $COMT^{LL}$ genotype than in the $COMT^{HH}$ genotype. In elderly men, COMT genotype was associated with an increased risk of self-reported fractures during their lifetime. In addition, $COMT^{LL}$ was found to be associated with increased E2 levels in middle-aged men and a decreased risk of myocardial infarction (MI) in middle-aged men and women combined.

In conclusion, the findings in this thesis indicate that COMT may be implicated in several physiological processes including the regulation of timing of puberty and growth in young girls and female mice, bone phenotype in young adult men, fracture risk in elderly men, the incidence of MI in middle-aged individuals, and serum E2 levels in middle-aged men.

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