

## COMT forms in L-dopa metabolism: a pharmacokinetic study in two types of transgenic mice

Käenmäki M, Tammimäki A, Männistö PT

Division of pharmacology and toxicology  
Faculty of pharmacy  
University of Helsinki

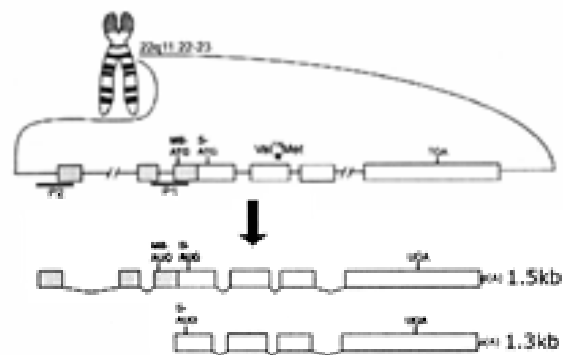


## Introduction

- Catechol O-methyltransferase (COMT) is a widespread enzyme that catalyses the methylation of compounds containing catechol structures
- One gene  $\Rightarrow$  two promoters  $\Rightarrow$  two separate enzymes
  - MB-COMT
  - S-COMT



## Comt gene



Tunbridge et al. Biol Psychiatry 60:141-151, 2006

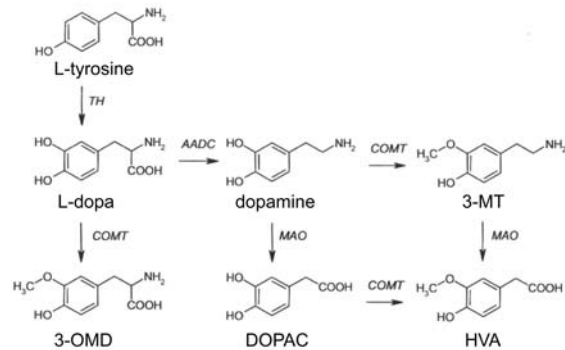


## S-COMT vs. MB-COMT

- |                                       |   |
|---------------------------------------|---|
| ■ "soluble"                           | ■ "membrane-bound"                                |
| ■ intracellular                       | ■ intracellular                                   |
| ■ cytoplasm or nucleus                | ■ membranes only                                  |
| ■ more abundant in peripheral tissues | ■ prevalence in the brain, particularly in humans |



## Dopamine metabolism



## Aims of the study

- Investigate the importance of the two forms of COMT in pharmacokinetics of L-dopa
- Give perspective of the importance of the two COMT forms (i.e. distribution of S-COMT and MB-COMT in the periphery or brain)



## Methods

- Animals
  - COMT deficient mice (COMT knock-out)
  - S-COMT deficient mice
  - wild-type mice
- Sample collection
  - levodopa (10 mg/kg) and carbidopa (30 mg/kg) was administered p.o. in 25 % CMC-suspension
  - blood samples: 0, 30, 60, 90 and 120 min  
⇒ plasma separated

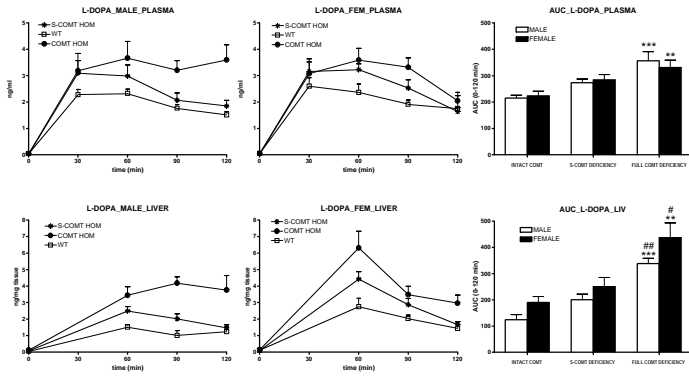


## Methods

- Tissue samples
  - liver
  - PFC
  - striatum
- Samples were analyzed for L-dopa, 3-OMD, DOPAC and HVA by HPLC equipped with electrochemical detection



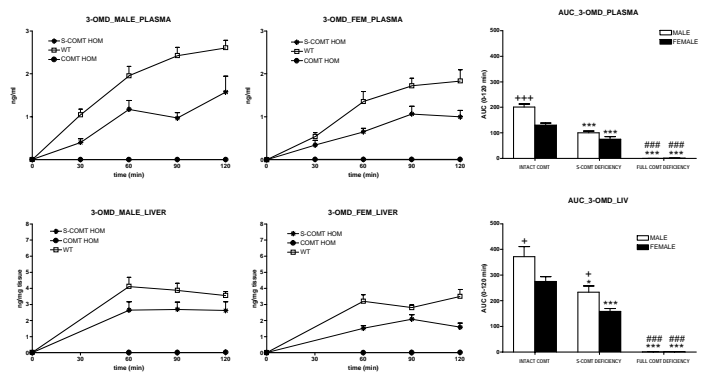
## Results - L-dopa



p\* compared to intact COMT, p# compared to S-COMT deficiency, n=6-13



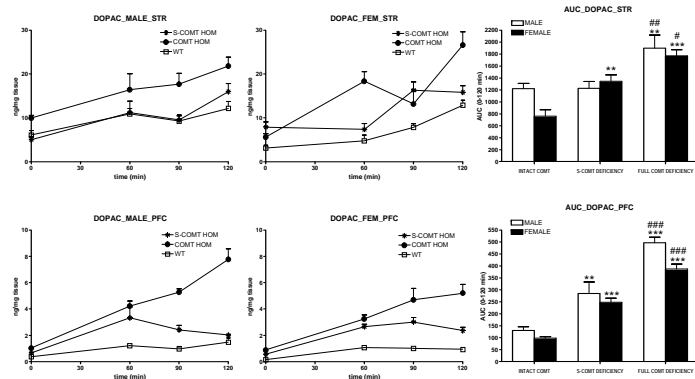
## Results - 3-OMD



p\* compared to intact COMT, p# compared to S-COMT deficiency, p+ compared to corresponding female, n=6-13



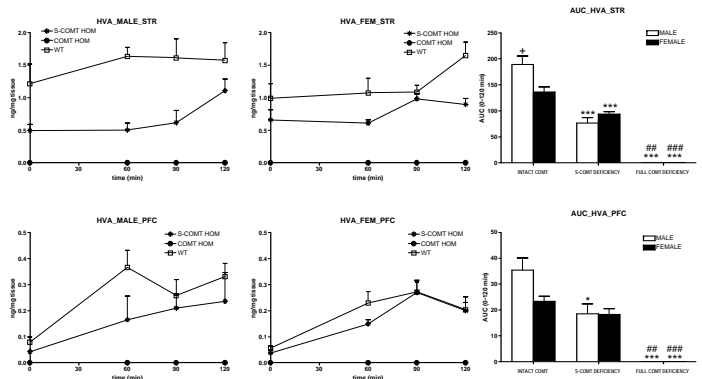
## Results - DOPAC



p\* compared to intact COMT, p# compared to S-COMT deficiency, n=6-13



## Results - HVA



p\* compared to intact COMT, p# compared to S-COMT deficiency, p+ compared to corresponding female, n=6-13



## Conclusions

- Lack of S-COMT had no significant effect on peripheral L-dopa levels
- Lack of COMT showed increased L-dopa levels whereas 3-OMD was absent
- Gender differences were found in L-dopa and 3-OMD levels



## Conclusions

- MB-COMT was responsible for approximately 50 % of the metabolism of L-dopa and dopamine both in peripheral and central tissues
- In the brain DOPAC levels were increased whereas HVA levels were decreased as a function of decreasing COMT activity



## Acknowledgements

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