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Effect of *Comt* gene disruption on brain dopamine

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COMT enzyme forms

- Membrane-bound (MB-COMT)
 - high affinity, low *O*-methylation capacity
 - dominant form in human brain
- Soluble (S-COMT)
 - low affinity, high capacity
 - dominant form in peripheral tissues


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The role of COMT in different brain areas

- Dopamine transporter (DAT) and subsequent oxidation by monoamine oxidase (MAO) are the primary means of clearing dopamine from the extracellular space.
- DAT density very high in the dorsal striatum, somewhat lower in the nucleus accumbens.
- DAT density low in the prefrontal cortex and hypothalamus.
- COMT mediated *O*-methylation has more importance in brain areas where DAT is sparse.

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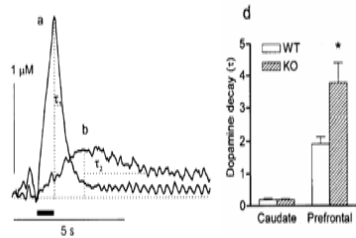
Effect of complete lack of COMT on baseline dopamine, DOPAC and HVA concentrations

- No effect on striatal, cortical or hypothalamic tissue or striatal extracellular dopamine levels
- DOPAC accumulates
- HVA below detection limit
- NO evidence of compensatory mechanisms
 - MAO-A and MAO-B
 - Phenylsulfotransferase
 - DAT

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Dopamine function in the prefrontal cortex of *Comt* gene disrupted mice

- Comt gene disruption profoundly affects DA clearing in the PFC
 - Amount of DAT is low -> 50 % of the DA decline mediated by COMT
 - COMT KO -/- males: 20-25 % increased stimulus-evoked DA release and two times slower elimination (Yavich et al., 2007)



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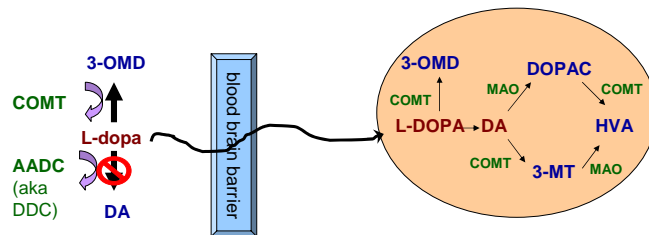
Effect of COMT deficiency on dopamine, DOPAC and HVA concentrations after carbidopa/levodopa (30/10 mg/kg i.p.)

- Hypothalamic and cortical, but not striatal, tissue dopamine levels elevated in COMT ko animals
- DOPAC accumulation accentuated
- HVA and 3-OMD not detectable in COMT ko brain tissue or extracellular fluid

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Aims

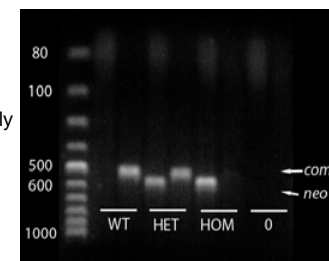
- To find out how the lack of S-COMT or both COMT isoforms affects the dopamine metabolism under normal conditions in dorsal striatum, nucleus accumbens and prefrontal cortex
- To elucidate the roles of S and MB-COMT in levodopa metabolism



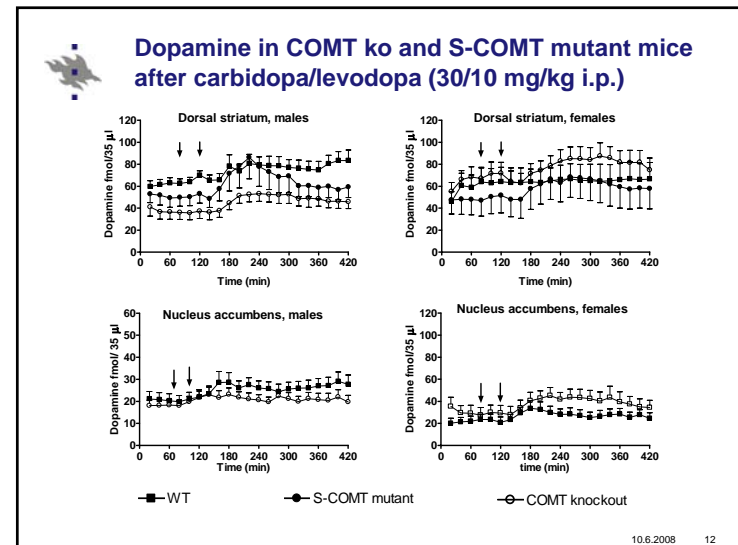
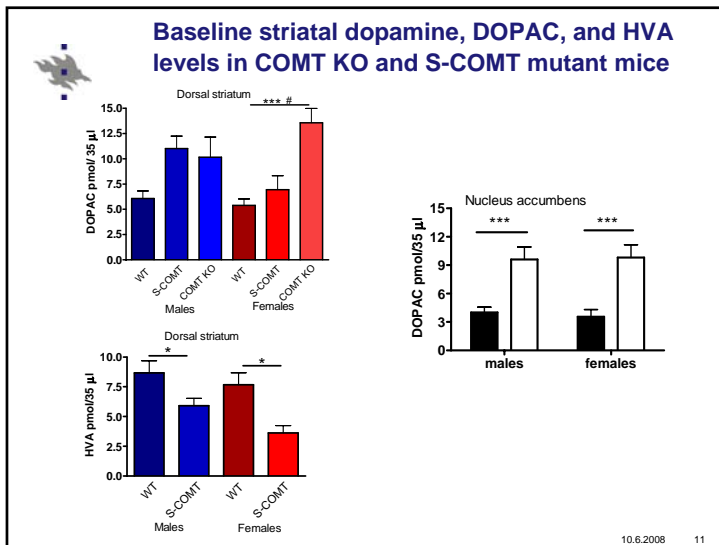
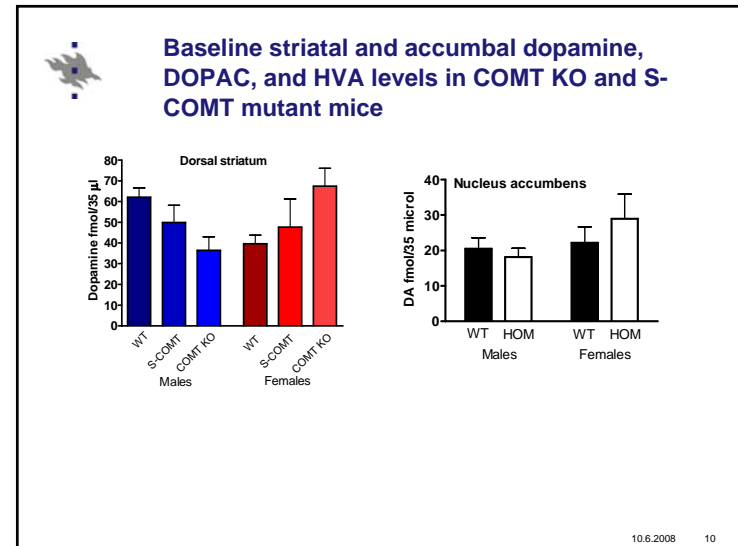
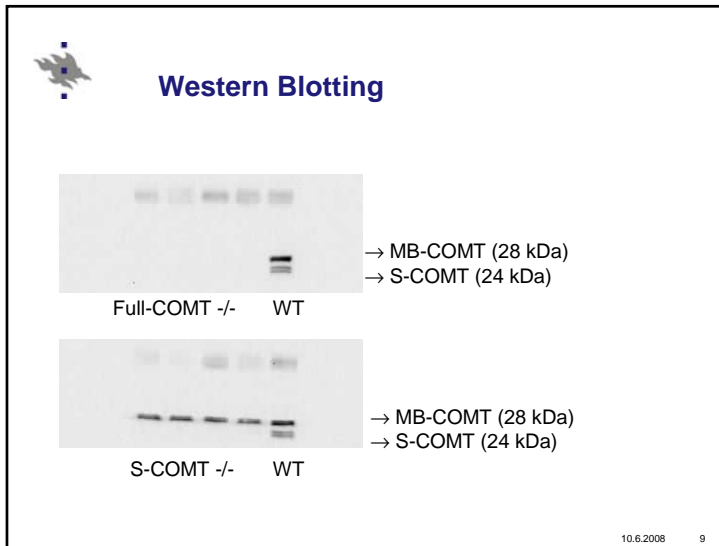
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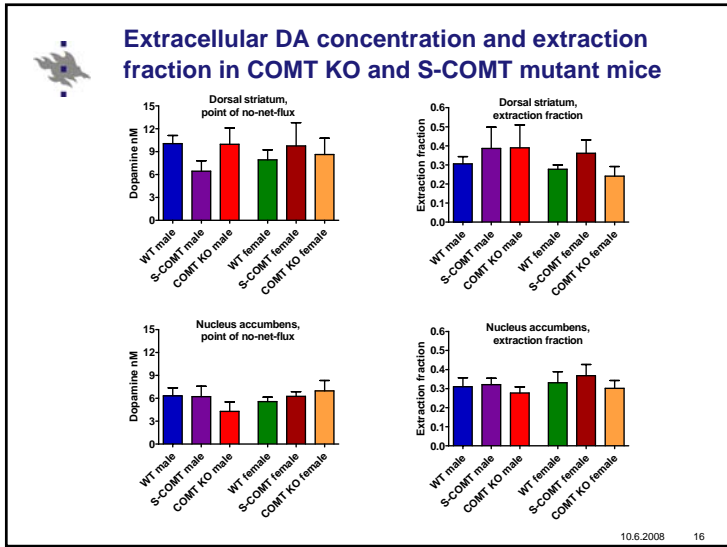
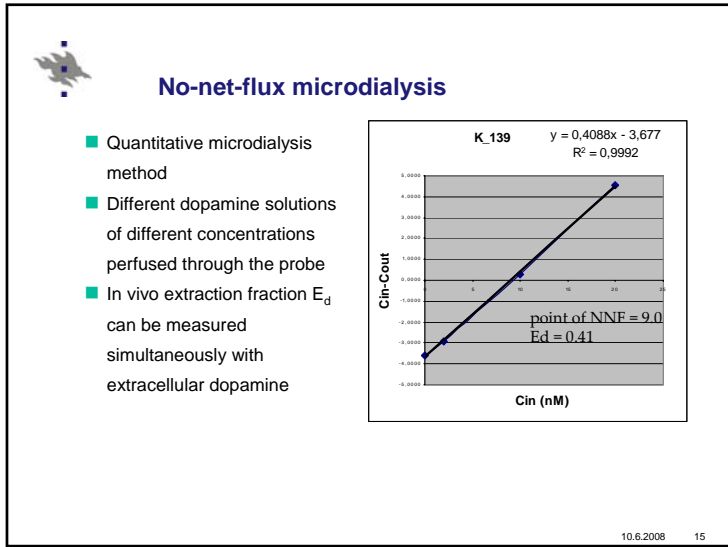
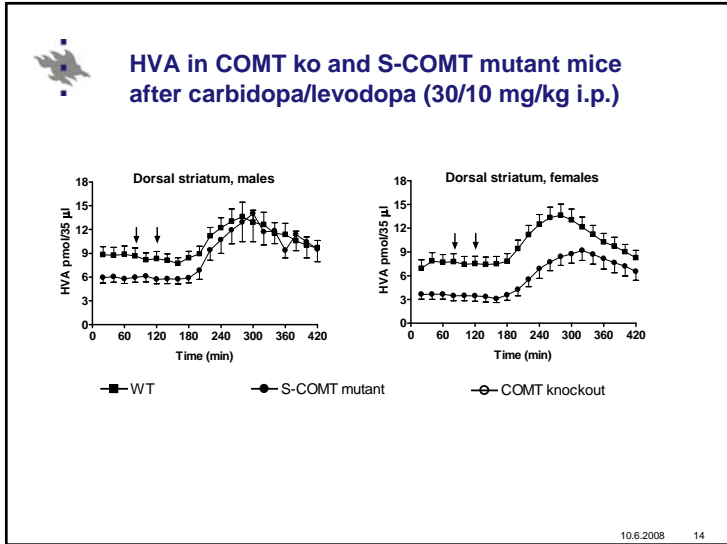
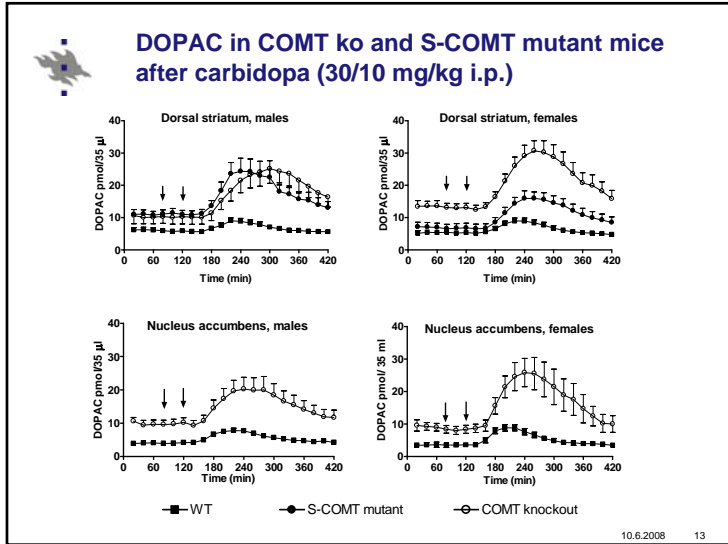
Mouse lines

- C57BL/6J background
- Full-COMT ko strain lacking both MB and S-COMT
- S-COMT mutant strain lacking only S-COMT



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Extracellular dopamine in PFC under levodopa load

- Differences in the basal dopamine and metabolite levels similar as in the dorsal striatum and nucleus accumbens
- Levodopa-induced increase in dopamine levels greater in all genotypes
- In homozygous *Comt* gene knockout males the dopamine concentration stays high longer

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Conclusions

- Lack of S-COMT or both COMT isoforms does not affect the extracellular concentration of dopamine in any brain area studied.
- S-COMT has a notable role in the O-methylation of dopamine or DOPAC in mouse brain. The role of S-COMT may, however, be different in male than in the female mice, and it may also be dependent on brain area.
- Even in prefrontal cortex, the uptake mechanisms and oxidation by MAO are efficient enough to maintain normal dopamine levels in the absence of COMT.

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