

CATECHOL-O-METHYLTRANSFERASE (COMT) INFLUENCES DOPAMINE METABOLISM OUTSIDE THE PREFRONTAL CORTEX



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LM Laatikainen^{1,2}, T Sharp², PJ Harrison¹ and EM Tunbridge¹
Departments of ¹Psychiatry and ²Pharmacology, University of Oxford, UK

Introduction

- Catechol-o-methyltransferase (COMT) metabolises catechol-containing compounds, including dopamine.
- COMT is genetically associated with dopamine-modulated cognitive and emotional phenotypes, and possibly with various psychiatric disorders.
- Most existing studies of COMT in this field have focused on the prefrontal cortex. However, COMT is widely expressed throughout the brain, particularly the hippocampus¹.

Aim

- To examine the acute effects of a centrally-acting COMT inhibitor, tolcapone, on dopamine metabolism in tissue homogenates of rat hippocampus, prefrontal cortex, striatum and cerebellum.
- To study both male and female rats, since COMT is sexually dimorphic².

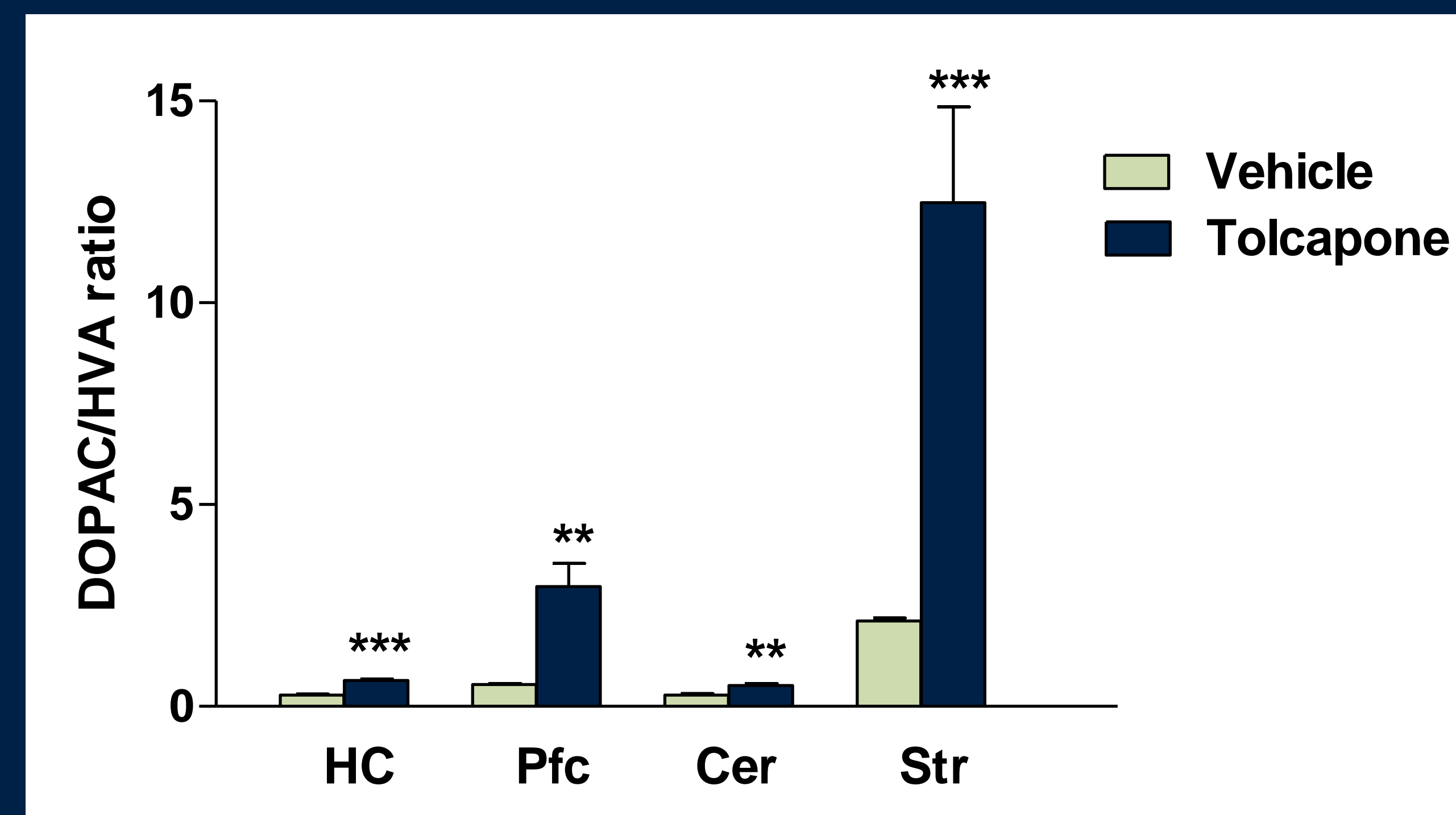
Results

Tolcapone affects dopamine metabolism throughout the brain

Across all brain regions studied:

Tolcapone

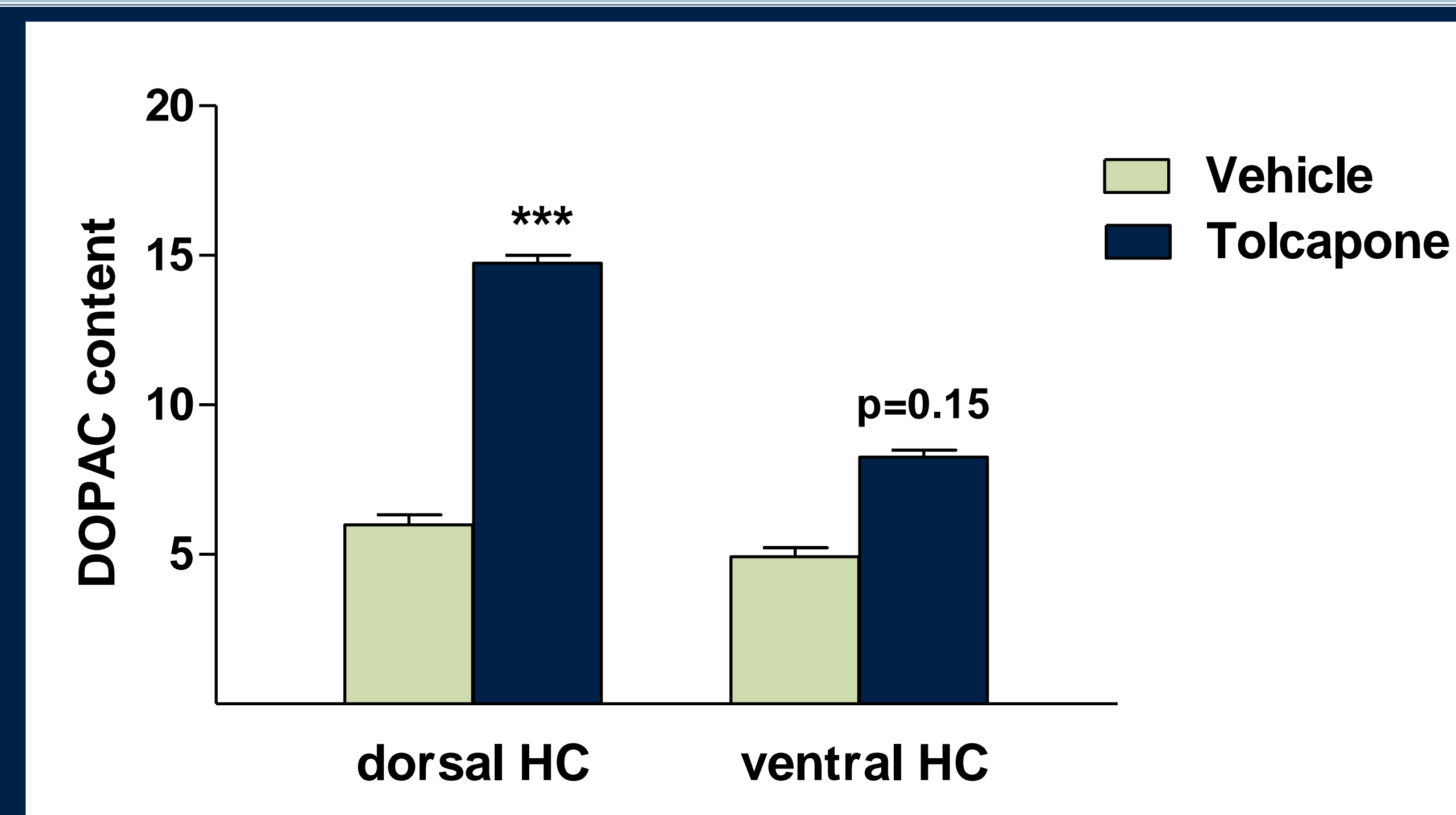
- Increased DOPAC ($p < 0.05$)
- Decreased HVA ($p < 0.001$)
- Increased DOPAC/HVA ($p < 0.001$)



Tolcapone affects DOPAC more in dorsal than ventral hippocampus

In hippocampal extracts:

Tolcapone increased DOPAC more in dorsal than ventral hippocampus (drug*region interaction, $p = 0.004$)



Tolcapone affects females more than males

Across all brain regions studied, the DOPAC/HVA data revealed a significant treatment*gender*region interaction ($p < 0.05$):

In striatum and prefrontal cortex, the effect of tolcapone on dopamine metabolism was more pronounced in females than males.

Methods

- 23 age-matched Lister hooded rats: female (128-154g, $n = 11$), male (202-230g, $n = 12$)
- Brain regions were dissected 2h after a single i.p. injection of tolcapone (30mg/kg, $n = 12$) or vehicle ($n = 10$)
- DOPAC and HVA levels were determined by HPLC-EC
- Analysis using ANOVAs with LSD post-hoc tests

Conclusions

- The COMT inhibitor, tolcapone had a significant effect on dopamine metabolism in all brain regions studied.
- These data suggest that **COMT plays an important role in regulating dopamine function throughout the brain**, including the hippocampus.
- The present data also highlight sexually dimorphic effects, as well differential effects between dorsal and ventral hippocampus, which warrant further investigation.
- The findings of this study may be relevant for the development of COMT inhibitors as potential treatment of dopamine dysregulation in disorders such as schizophrenia.

Abbreviations

Cerebellum (Cer), hippocampus (HC), prefrontal cortex (Pfc) and striatum (Str).

References

1. Matsumoto M et al. *Neuroscience* 2003; 116(1): 127-37.
2. Harrison PJ, Tunbridge EM. *Neuropsychopharmacology* 2008; 33(13), 3037-45.

Acknowledgements

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