Brain-derived neurotrophic factor genotype status impacts on hippocampal serotonin 5-HT1A receptor binding

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Background: Existing evidence indicates a tight interconnection between serotonin (5-HT) and brain derived neurotrophic factor (BDNF). A functional polymorphism in the promoter region of the BDNF gene (Val66Met), resulting in reduced extracellular BDNF levels in Met carriers, was previously demonstrated to impact on the 5-HT transporter but not the 5-HT1A receptor in humans [1]. However, recent studies show that reduced BDNF levels affect especially hippocampal 5-HT1A functionality [2,3]. The aim of this work was to closer investigate the impact of the Val66Met polymorphism on subcortical 5-HT1A binding in humans by positron emission tomography (PET).

Methods: Thirty-four healthy subjects from our existing PET database (19 female, 36.4 ± 10.4; 15 male, 37.7 ± 8.7) were matched according to sex, age and BDNF Val66Met genotype status. All subjects underwent PET using the 5-HT1A-selective radiotracer [carbonyl-11C]WAY-100635. DNA was extracted from peripheral blood monocyte cells obtained by 9 ml EDTA blood samples using the QIAamp DNA Mini Kit (QIAGEN®). Genotyping was performed for Val66Met (rs6265) using the MassARRAY platform (SEQUENOM®). PET data were spatially normalized to standard MNI space and 5-HT1A receptor binding potential was calculated. A subcortical mask was designed for both hippocampi, amygdalae, insulae and anterior cingulate cortices. Differences in 5-HT1A binding were assessed by ANOVA calculated in SPM8 and corrected for multiple comparisons using family-wise error rate (FWE).

Results: A significant main effect was found in the left hippocampus (p = 0.02). We observed higher 5-HT1A binding in Met allele carriers compared to Val homozygotes in the left (p = 0.017) and right (p = 0.038) hippocampus. No further region exhibited significant results. Although there was no significant sex × genotype interaction (p = 0.08), we detected significantly less 5-HT1A binding in female Val homozygotes than in male in the left (p = 0.03) and right (p = 0.032) hippocampus. There was no difference between female and male Met carriers.

Discussion: These results demonstrate an impact of BDNF genotype status on hippocampal 5-HT1A receptor binding underlining strong crosslinks between BDNF and the serotonergic system. Female Val carriers exhibited the least amount of hippocampal 5-HT1A binding which is in line with previous evidence showing sex effects of the BDNF × 5-HT interaction. While our dataset points towards elevated hippocampal 5-HT1A binding upon BDNF impairment, the molecular mechanisms of this interaction are assumingly complex and still unresolved.

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References

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