Association between Catechol-O-methyltransferase Genotype and Serotonin-1A Receptor Binding using Positron Emission Tomography

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AIM OF THE STUDY:
The enzyme Catechol-O-methyltransferase (COMT) is responsible for the degradation of catecholamines, e.g. dopamine and noradrenaline. The functional single-nucleotide-polymorphism rs4680, resulting in a valine to methionine mutation at position 158 (Val158Met) of the COMT gene, has been associated with several psychiatric conditions such as depression, anxiety disorders and schizophrenia [1]. In recent years, several neuroimaging studies using positron emission tomography (PET) described a novel “endophenotype” underlying major depressive disorder (MDD), corresponding to a reduced 5-HT1A receptor binding in distinct subcortical and cortical brain regions involved in emotional and cognitive processing in affected persons compared to healthy subjects. A number of genetic variants of the serotonergic system have been shown to influence 5-HT1A receptor binding and thereby adjudicated a certain role in the development of depression. Here, the aim was to assess the potential impact of rs4680 on 5-HT1A receptor binding using PET in vivo.

RESULTS:
Among the study population including 52 healthy subjects (38, 40.48 ± 15.01years, mean age ± SD) were measured once using PET and the selective 5-HT1A receptor antagonist [carbonyl-11C]WAY-100635 as radioligand. Additionally, 8ml EDTA blood samples were drawn from each participant. DNA was purified from whole blood according to the QIAGEN® QIAamp DNA Mini Kit handbook. Genotyping was performed for COMT rs4680 using a matrix-assisted laser desorption/ionization mass spectrometry and the software AssayDesign 3.1 (SEQUENOM®). PET data were corrected for head motion and normalized to MNI space (SPM8). 5-HT1A receptor quantification (BPND) was achieved following a voxel-wise approach using MRTM2 in PMOD 3.3 (reference=cerebellar gray matter excl. vermis). For statistical analysis in SPM8, ANOVA was applied with a post-hoc t-test contrasting 5-HT1A receptor binding potential of all A carriers (AA+AG, 43 subjects) against homozygote G carriers (9 subjects), respectively.

METHODS:
25 healthy subjects (38, 40.48 ± 15.01years, mean age ± SD) were measured once using PET and the selective 5-HT1A receptor antagonist [carbonyl-11C]WAY-100635 as radioligand. Additionally, 8ml EDTA blood samples were drawn from each participant. DNA was purified from whole blood according to the QIAGEN® QIAamp DNA Mini Kit handbook. Genotyping was performed for COMT rs4680 using a matrix-assisted laser desorption/ionization mass spectrometry and the software AssayDesign 3.1 (SEQUENOM®). PET data were corrected for head motion and normalized to MNI space (SPM8). 5-HT1A receptor quantification (BPND) was achieved following a voxel-wise approach using MRTM2 in PMOD 3.3 (reference=cerebellar gray matter excl. vermis). For statistical analysis in SPM8, ANOVA was applied with a post-hoc t-test contrasting 5-HT1A receptor binding potential of all A carriers (AA+AG, 43 subjects) against homozygote G carriers (9 subjects), respectively.

CONCLUSIONS:
Our findings indicate that homozygote G carriers (Val/Val) for the COMT Val158Met variant exhibit a higher 5-HT1A receptor binding than A carriers in the PCC, a region designated to the default mode network, which is responsible for self-perception and frequently reported to be altered in MDD. Based on the insight that MDD comes along with cognitive deficits, the present results suggest a possible mediation of these symptoms via rs4680. This is in line with functional magnetic resonance imaging (fMRI) studies emphasizing a modulating role of the COMT gene in cognitive processes given its major function as dopamine degrading enzyme in the prefrontal cortex. Accordingly, the impact of Val/Val genotype was also determined for the PCC showing a greater deactivation in this region in healthy volunteers performing memory tasks [2]. Furthermore, the interplay of dopaminergic and serotonergic neurotransmission has been proposed as potential mechanism underlying anhedonia, and previous findings suggest a role for COMT in vulnerability to disorders etiologically based on altered serotonergic neurotransmission [3]. Present results suggest a further association of rs4680 and 5-HT1A receptor, indicating an interaction of introspection, cognition and emotion processing.

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References:

Figure 1. Differences in serotonin-1A receptor binding potential between AA+AG versus GG genotype carriers of the rs4680, presented on an axial and sagittal view, superimposed on a structural magnetic resonance image. Shown are post-hoc t-test values of the ANOVA (voxel-level p<0.01 uncorrected, k>2.4, cluster-level p<0.05 FWE corrected, k>1293). The peak value can be observed in the posterior cingulate cortex (x/y/z=10/-40/36mm, MNI space). The color table indicates the t-values. Cross is located at x/y/z=3/-42/4mm (MNI space).

Figure 2. Scatter plot showing the mean serotonin-1A receptor binding potential for each genotype of rs4680 in the posterior cingulate cortex (x/y/z=10/-40/36mm, MNI space). Binding potential values are highest for homozygote GG carriers (N=9) of the rs4680, where A carriers (AA, N=10; AG, N=33) display significantly lower values, for both applies p<0.001. There is no significant difference between AA and AG carriers (p>0.1).