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COMT Val¹⁵⁸Met genotype and striatal D_{2/3} receptor binding in adults with 22q11 deletion syndrome

Submitted

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SUMMARY

Although catechol-*O*-methyltransferase (COMT) activity evidently affects dopamine function in prefrontal cortex, the contribution in striatum is assumed less significant. We studied whether a functional polymorphism in the COMT gene (Val¹⁵⁸Met) influences striatal D_{2/3}R binding ratios (D_{2/3}R BP_{ND}) in fifteen adults with 22q11 deletion syndrome, hemizygous for this gene, using single photon emission computed tomography (SPECT) and the selective D_{2/3} radioligand [¹²³I]IBZM. Met hemizygotes had significantly lower mean D_{2/3}R BP_{ND} than Val hemizygotes. These preliminary data suggest that low COMT activity may affect dopamine levels in striatum and may have implications for understanding the contribution of COMT activity to psychiatric disorders.

INTRODUCTION

Catechol-O-methyltransferase (COMT) is one of the major enzymes involved in dopamine (DA) elimination in human brain. Along with DA uptake by the dopamine transporter, COMT activity is considered to be essential in the regulation of synaptic DA levels. Two aspects of COMT function are important to consider. Firstly, the COMT gene contains a common single nucleotide polymorphism, a valine-to-methionine substitution (Val¹⁵⁸Met), changing enzyme activity. The relatively unstable Met allele is associated with considerable lower enzymatic activity than the Val allele [13]. Secondly, previous studies suggest regional differences in the contribution of COMT to the regulation of synaptic DA levels [8]. Notably, there is robust evidence that COMT activity crucially affects DA metabolism in prefrontal cortex. In contrast, in striatum COMT is assumed to play a less significant role [13] and previous studies in healthy subjects did not demonstrate an influence of this polymorphism on striatal DA function [8,12].

The COMT gene is located at chromosomal region 22q11, which is deleted in people with 22q11 deletion syndrome (22q11DS). People with 22q11DS carry only one copy of this gene and could be expected to have low COMT activity, resulting in abnormal DA function [2]. In addition, 22q11DS is characterized by a high rate of several psychiatric disorders, including schizophrenia, obsessive compulsive disorder, attention deficit hyperactivity disorder and affective disorders [5].

In this study, we report on the COMT Val¹⁵⁸Met genotype and striatal D_{2/3} receptor (D_{2/3}R) binding ratios in adults with 22q11DS. We hypothesized that Met hemizygotes have higher synaptic DA levels in striatum with consequently lower mean striatal D_{2/3}R binding ratios than Val hemizygotes.

MATERIALS AND METHODS

Fifteen antipsychotic and psychostimulant naive adults (18-43 years old) with 22q11DS, with no current or past psychiatric history, completed the study. Findings from 12 subjects were published previously [3]. Protocol approval, inclusion/exclusion criteria, informed consent procedure, assessment of full-scale intelligence (FSIQ) and COMT Val¹⁵⁸Met genotype analysis were as described previously. We assessed striatal D_{2/3}R binding ratios (BP_{ND}) in all subjects with [¹²³I]IBZM SPECT using the validated equilibrium/constant infusion technique. The SPECT protocol, image reconstructions and analysis were all performed as described in our previous report [3]. To refine the relation between DA function and neuropsychiatric symptoms, clinical symptoms associated with DA neurotransmission were also evaluated in all subjects. Positive and negative symptoms and general psychopathology were assessed with the Positive and Negative Syndrome Scale (PANSS) [10], obsessive compulsive symptoms were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [7], impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11) [11], and depressive symptoms were assessed with the Beck Depression Inventory (BDI-II) [1]. Between-group (Val versus Met hemizygotes) differences for sex distribution were tested by Fisher's Exact Test. Between-group

differences in $D_{2/3}R$ BP_{ND} and scores on the PANSS, Y-BOCS, BIS-11 and BDI-II were tested by Mann-Whitney Test. Correlations between clinical parameters and $D_{2/3}R$ BP_{ND} were tested using Spearman's rank correlation coefficient.

RESULTS

Subject characteristics

The groups did not differ significantly in gender distribution (10 Met hemizygotes (3 males, 7 females), 5 Val hemizygotes (3 males, 2 females) (Fisher's Exact Test, $P = 0.33$)), in age (mean (s.e.m.): Met hemizygotes 28.0 (2.3) years, Val hemizygotes 30.2 (4.2) years, or in FSIQ (Met hemizygotes 77.9 (2.8), Val hemizygotes 74.2 (6.3)). Except for significantly lower mean (s.e.m.) scores (67.3 (1.9)) on the BIS-11 in Met hemizygotes compared to Val hemizygotes (78.4 (4.2), $P = 0.02$), there were no differences on the other clinical variables.

SPECT Results and relations with clinical measures

Met hemizygotes showed significantly lower mean (s.e.m.) $D_{2/3}R$ BP_{ND} (1.10 (0.04)) than Val hemizygotes (1.33 (0.08)) in striatum (Mann-Whitney Test, $P = 0.04$) (**figure 1**). There were no significant correlations between $D_{2/3}R$ BP_{ND} and any of the clinical variables for the 22q11DS subjects as a whole group.

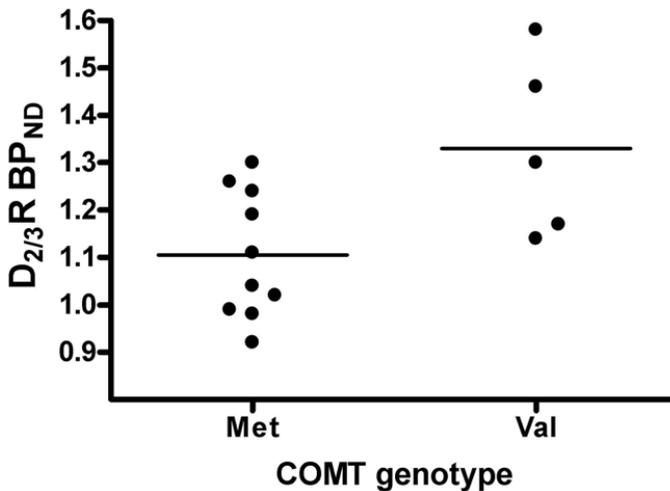


Figure 1.

COMT Val¹⁵⁸Met polymorphism and mean striatal $D_{2/3}$ receptor binding ratios ($D_{2/3}R$ BP_{ND}) in adults with 22q11 deletion syndrome.

DISCUSSION

The main finding of this study is that Met hemizygous adults with 22q11DS showed significantly lower mean D_{2/3}R BP_{ND} in striatum than Val hemizygotes. Lower mean D_{2/3}R BP_{ND} may reflect higher synaptic DA levels in the Met hemizygotes. This would be consistent with lower COMT activity in Met hemizygotes accompanied by less DA clearance.

Why is it that the present study shows influence of the COMT Val¹⁵⁸Met polymorphism on striatal D_{2/3}R BP_{ND} while previous studies [8,12], in human subjects without 22q11DS, did not? The most plausible explanation would be that in subjects with 22q11DS, because they are haplo-insufficient for the COMT gene, small genetic variations like the Val¹⁵⁸Met polymorphism, have a relatively large impact on enzyme activity. Yet, in our original sample, the 22q11DS subjects did not show different mean striatal D_{2/3}R BP_{ND} in comparison with healthy subjects [3]. However, in that study Val and Met hemizygotes were analyzed together as one group. In contrast to 22q11DS, it is plausible that in healthy subjects, who are bi-allelic [8,12], the effect of Val¹⁵⁸Met polymorphism on COMT activity is too small to influence striatal DA levels, or striatal D_{2/3}R binding, significantly. Herewith, it is important to consider that relatively large differences in endogenous DA may be needed before differences become apparent with techniques like SPECT.

Preceding preclinical studies also failed to show influence of COMT activity on striatal DA function under normal conditions [4,6,9]. However, caution has to be taken when extrapolating the results from rodent studies to humans. Metabolism of DA differ between species [9] and the contribution of COMT on DA elimination in human striatum is possibly larger than would be expected from rodent studies [9].

The following limitations of the present study should be considered. Small sample sizes and dimorphic gender effects on COMT function [6,8] may have influenced the results. In future studies, more 22q11DS subjects matched for age and sex should be included with an equal distribution of COMT Val¹⁵⁸Met genotype.

It should be noted that, like other human studies, this study was performed at a resting state. However, it is possible that under challenged conditions relatively small differences in COMT activity become more important. For example, greater increases in striatal DA levels were found in COMT inhibited rats [4] challenged with levodopa, as compared with the wild types. Thus, it is still imaginable that, also in healthy subjects, striatal DA levels are not dependent on COMT Val¹⁵⁸Met polymorphism under normal conditions, whereas they are when DA release is greater, like in challenged situations. In addition to lower D_{2/3}R BP_{ND} in the Met hemizygous adults compared to Val hemizygotes, Met hemizygotes showed lower scores on the BIS-11 than Val hemizygotes (lower scores indicate less impulsivity). We did not find differences between Met and Val hemizygotes on any of the other clinical measures. However, it has to be noted that subjects with a psychiatric history were excluded from this study. In addition, it should be recognized that differences in complex brain functions are not simply the effect of a single nucleotide polymorphism.

In conclusion, our preliminary data suggest that COMT activity may affect DA levels in striatum in 22q11DS. Although we did not find any relations between $D_{2/3}$ receptor binding ratios in striatum and clinical measures, these results may possibly contribute to improved understanding of the relation between COMT activity and (ab)normal brain function.

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DECLARATION OF INTEREST

None.

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