COMT Val¹⁵⁸Met Genotype and Striatal D_{2/3} Receptor Binding in Adults with 22q11 Deletion Syndrome

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ABSTRACT

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 and 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 in humans and this 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 (Tunbridge et al., 2006). Secondly, previous studies suggest regional differences in the contribution of COMT to the regulation of synaptic DA levels (Hirvonen et al., 2010). 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 (Tunbridge et al., 2006) and previous studies in healthy subjects did not demonstrate an influence of this polymorphism on striatal DA function (Hirvonen et al., 2010; Slifstein et al., 2008). However, other studies suggest that under specific circumstances COMT activity may possibly influence striatal DA function (Brannan et al., 1992; Ceravolo et al., 2002) (see for details discussion section).

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 (Boot et al., 2008). In addition,

22q11DS is characterized by high rates of several psychiatric disorders, including schizophrenia, obsessive compulsive disorder, attention deficit hyperactivity disorder and affective disorders (Fallgatter and Lesch, 2006).

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-naïve adults (18-43 years old) with 22q11DS, with no current or past psychiatric history, completed the study. Findings from 12 subjects were published previously (Boot et al., 2010). Protocol approval, inclusion/exclusion criteria, informed consent procedure, assessment of full-scale intelligence (FSIQ) and COMT Val¹⁵⁸Met genotype analysis were as described previously (Boot et al., 2008; Boot et al., 2010). 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 (Boot et al., 2010). 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) (Kay et al., 1987), obsessive compulsive symptoms were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995), and depressive symptoms were assessed with the Beck Depression Inventory (BDI-II) (Beck et al., 1996). 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 U 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 in 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 (Fig. 1; Mann-Whitney Test, $P = 0.04$; individual data in Table 1). No difference in striatal $D_{2/3}R$ BP_{ND} was found between males and females ($P = 0.81$). 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.

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 (Hirvonen et al., 2010; Slifstein et al., 2008), in healthy human subjects without 22q11DS, did not? Possibly, in subjects with 22q11DS who are hemizygous for the COMT gene, small genetic variations like the Val¹⁵⁸Met polymorphism, may have a relatively large impact. With respect to COMT activity, the COMT Val¹⁵⁸Met alleles exert a co-dominant effect resulting in a gene-dose relationship (Tunbridge et al., 2006). For example, healthy subjects without 22q11DS with the Val/ Met genotype display an intermediate level of COMT enzyme activity in between individuals homozygous for the Met and Val enzyme variants. Moreover, over-expression of COMT is associated

with enhanced COMT activity (Suzuki et al., 2009), and hemizyosity for the COMT gene is associated with reduced COMT gene expression (van Beveren et al., 2007). Thus, in 22q11DS, the Val¹⁵⁸Met polymorphism may have a critical effect, because only one copy of the COMT gene is present (no compensating allele). However, to the best of our knowledge, there is no direct evidence to support this assumption. In our original sample, 22q11DS subjects (Val and Met hemizygotes combined) did not show different mean striatal D_{2/3}R BP_{ND} in comparison with healthy subjects (Boot et al., 2010). In that study, however, effect of COMT genotype was not studied. In contrast to 22q11DS, it is plausible that in healthy subjects, who are bi-allelic (Hirvonen et al., 2010; Slifstein et al., 2008), 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 IBZM SPECT.

Preceding preclinical studies also failed to show influence of COMT activity on striatal DA function under normal conditions (Brannan et al., 1992; Gogos et al., 1998; Huotari et al., 2002). However, caution has to be taken when extrapolating the results from rodent studies to humans. Metabolism of DA differs between species (Huotari et al., 2002) and the contribution of COMT on DA elimination in human striatum is possibly larger than would be expected from rodent studies (Huotari et al., 2002).

It should be noted that, like the abovementioned human studies, our study was performed at a resting state. However, it is possible that under challenged conditions differences in COMT activity become more important. For example, greater increases in striatal DA levels were found in COMT inhibited rats (Brannan et al., 1992) challenged with levodopa, as compared with the wild types. Similarly, patients with Parkinson's disease that add tolcapone, a potent and selective inhibitor of COMT, to their treatment with levodopa / carbidopa, demonstrate reduced striatal DA catabolism, compared to patients on levodopa / carbidopa that did not receive tolcapone (Ceravolo et al., 2002). Thus, it is possible that striatal DA levels are not dependent on COMT Val¹⁵⁸Met polymorphism under normal conditions, whereas they are when DA release is greater, like in 22q11DS and or in challenged conditions.

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.

The following limitations of the present study should be considered. Small sample sizes and dimorphic gender effects on COMT function (Gogos et al., 1998; Hirvonen et al., 2010) may have influenced the results. Interestingly, COMT appears to differentially impact on brain function in males and females (Harrison and Tunbridge, 2008). Thus, although in the present study the groups did not differ significantly in gender distribution and we did not find a significant effect of gender on striatal $D_{2/3}$ receptor binding, we cannot rule out the possibility that the between-group differences in $D_{2/3}R$ BP_{ND} were a result of (COMT-related) gender dimorphisms. Ideally, in future studies, more 22q11DS subjects matched for age and sex should be included with an equal distribution of COMT Val¹⁵⁸Met genotype.

For interpretation of studies on the COMT Val¹⁵⁸Met genotype, including the present work, it should also be considered that complex brain functions will not be explained by single polymorphisms alone.

Other polymorphic variations in the COMT gene, and epistatic interactions with other candidate genes e.g. polymorphisms in the DRD2 gene, may have influenced our findings.

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

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Subject	COMT genotype	Gender	D _{2/3} R BP _{ND}
1	Met	F	1.19
2	Met	M	0.92
3	Met	F	1.24
4	Met	F	1.30
5	Met	F	0.98
6	Met	F	1.04
7	Met	M	0.99
8	Met	F	1.02
9	Met	M	1.11
10	Met	F	1.26
11	Val	M	1.46
12	Val	M	1.58
13	Val	F	1.30
14	Val	F	1.17
15	Val	M	1.14

Tab. 1. COMT Val¹⁵⁸Met polymorphism, gender and striatal D_{2/3} receptor binding ratio (D_{2/3}R BP_{ND}) for each study subject.

Fig. 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.