DRD2/ANKK1 Taq1A polymorphism (rs1800497) has opposing effects on $D_{2/3}$ receptor binding in healthy controls and patients with major depressive disorder

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Abstract

The A1 allele of the DRD2/ANKK1 Taq1A polymorphism (rs1800497) is associated with reduced striatal $D_{2/3}$ receptor binding in healthy individuals (Con) as well as depression and addiction. However, the effect of rs1800497 on $D_{2/3}$ receptor binding in depressed patients as well as the SNP's effect on $D_{2/3}$ binding during reward-associated dopamine release is unknown. Twelve unmedicated patients with major depressive disorder (MDD) and 24 Con completed PET scans with [^{11}C]raclopride, once without receiving monetary rewards (baseline) and once while winning money. In Con, the A1 allele was associated with reduced baseline binding potential (BP_{ND}) in the middle caudate and ventral striatum. However, in MDD patients the A1 allele was associated with increased baseline BP_{ND} in these regions. There were no significant associations between rs1800497 and change in BP_{ND} during reward-associated dopamine release. Conceivably, the A1 allele predisposes to depression and addiction via its effect on the post-synaptic D_2 receptor.

Keywords

Depression; dopamine 2 receptor; positron emission tomography; reward; Taq1A

Introduction

The majority of dopamine (DA) D_2 receptors are densely distributed on post-synaptic, non-dopaminergic neurons in the striatum where D_2 signalling modulates a variety of functional domains, including reward processing and appetitive behaviour. Additionally, D_2 autoreceptors located in the somas, dendrites and terminals of DA neurons in the ventral tegmentum negatively regulate DA signalling by modulating firing rate (Ford et al., 2010), and DA release and synthesis (Wolf and Roth, 1990), respectively. A widely studied single nucleotide polymorphism (SNP), the so-called DRD2/ANKK1 Taq1A polymorphism (rs1800497, Glu[713]Lys) is located ~10 kb downstream from the DRD2 gene in the ankyrin repeat and kinase domain containing 1 (*ANKK1*) gene.

The A1 allele of rs1800497 has consistently been implicated in addiction disorders (Noble, 2000; Smith et al., 2008; Chen et al., 2011) and has also been reported to be a risk factor for depression, possibly via its impact on the quality of early parental interactions. Mills-Koonce et al. (2007) reported that children with the A1 allele showed more negative emotions during interactions with their parents, an effect that was attenuated by maternal sensitivity. Consistent with these data, the A1 allele was associated with 'social problems' as measured by the Child Behaviour Checklist questionnaire in children with reading disorders (Marino et al., 2004). In another study the A1 allele was associated with emerging symptoms of anxiety and depression as well as parent× child interactions characterized by negative emotions (Hayden et al., 2010). Similarly, children aged 10–12 yr with the A1 allele were more sensitive to negative feedback during a probabilistic learning task (Althaus et al., 2009). The putative effect of the A1 allele on childhood behaviour and depression may arise from basic physiological differences in the ability to regulate emotions that are present very early in development. Infants aged 3 and 6 months with the A1 allele, who were separated from their parents in an experimental setting, showed reduced ability to regulate vagal tone compared to infants without an A1 allele (Propper et al., 2008). In a longitudinal study of 2347 adult males, the A1 allele was associated with an increased risk of developing depressive symptoms at follow-up (odds ratio 2.55; Roetker et al., 2012). Consistent with these data, veterans with post-traumatic stress disorder who carried the A1 allele had more symptoms of anxiety, depression and social dysfunction than A2/A2 homozygotes (Lawford et al., 2006).

The Taq1A polymorphism or a variant in linkage disequilibrium with Taq1A appears to affect D_2 receptor binding, perhaps explaining the reported associations between Taq1A and psychiatric and addiction disorders. Relative to the A2 allele, the A1 allele has been associated with reduced striatal glucose metabolism (Noble et al., 1997) and reduced binding of the $D_{2/3}$ receptor antagonist, [11C]raclopride, in studies of healthy subjects (Thompson et al., 1997; Pohjalainen et al., 1998; Jonsson et al., 1999). In addition, the DRD2 C957T SNP, which may be in linkage disequilibrium (LD) with rs1800497 (Hirvonen et al., 2009), reportedly affects striatal $D_{2/3}$ receptor binding in healthy volunteers (Hirvonen et al., 2004).

Although genetic studies have implicated the TaqA1 allele in susceptibility to depression and the TaqA1 allele has been associated with reduced D_2 receptor binding in healthy controls, it is unknown how the TaqA1 allele would affect D_2 receptor binding in patients with mood disorders. As we reported in our recent review of the positron emission tomography (PET) D_2 literature, the data are contradictory and arguably the weight of data is suggestive of increased D_2 receptor binding in mood disorders (Savitz and Drevets, 2013). For example, compared with healthy controls, unmedicated patients with major depressive disorder (MDD) and motor retardation displayed increased [11C]raclopride binding potential (BP_{ND}) in the caudate and striatum (Meyer et al., 2006) and Kestler et al. (2000) reported a

positive correlation between $[^{11}C]$raclopride binding in the striatum and the 'depression' subscale score of the NEO Personality Inventory. Similarly, an increase in striatal D_2 receptor binding in depression was reported in single photon emission tomography studies using the radioligand, ^{123}I-iodobenzamide (D'Haenen and Bossuyt, 1994; Shah et al., 1997). Potentially consistent with these data, rats exposed to chronic social stress display elevated D_2 receptor binding in the striatum (Lucas et al., 2004; although see (Zhu et al., 2011) who report decreased stress-associated D_2 mRNA expression in the striatum. Nevertheless, it is conceivable that the elevations of D_2 receptor availability and increased $[^{11}C]$raclopride binding observed in depressed humans and in rodent depression analogues may arise secondarily to reductions in baseline DA release, consistent with the decreased basal firing activity of DA neurons in rats studied in depression models (Chang and Grace, 2012).

In order to investigate the apparent contradiction between the genetic association studies that implicate the A1 allele in depression, and some of the *in vivo* human and animal studies that are suggestive of increased D_2 receptor binding in MDD or rodent analogues thereof, we measured the effect of the Taq1A SNP on D_2 receptor BP_{ND} in both healthy volunteers and unmedicated patients with MDD.

Furthermore, in contrast to previous studies that measured the effect of the Taq1A SNP on D_2 receptor binding at rest only (i.e. during tonic DA release), we also tested the effect of the Taq1A SNP on D_2 receptor BP_{ND} during receipt of unpredicted reward (i.e. during phasic DA release). We were able to do this by scanning subjects under two conditions during PET$[^{11}C]$raclopride imaging. In the first condition the subjects played a slot machine task without receiving monetary rewards (baseline condition) and in the second, subjects received unpredictable monetary rewards while performing the identical slot machine task (reward condition). This approach yielded two measures of striatal DA transmission: (1) $D_{2/3}$ receptor BP_{ND} in the striatum at baseline; (2) the effect of endogenous DA released from DA neurons, measured as the percentage decrease in $[^{11}C]$raclopride BP_{ND} between baseline and reward PET images (ΔBP_{ND}).

Method

Detailed descriptions of the subject sample, gambling task and the PET imaging methodology have been previously published (Martin-Soelch et al., 2011). Briefly, medically and psychiatrically-healthy volunteers [n=24, 11 males, aged 35±8 yr, (MADRS) score=0.56±1.5, 42% white, 25% black, 13% Hispanic, 17% Asian, 3% other] and medically healthy patients who met DSM-IV-TR criteria for MDD (current depressive episode; n=12, 4 males, aged 38±11yr, MADRS score= 24.5±7.3, 50% white, 25% black, 8% Hispanic, 8% Asian, 8% other) and who had not used tobacco for at least 1 yr, had no history of substance dependence, substance abuse within 1 yr or pathological gambling behaviour underwent PET-$[^{11}C]$raclopride imaging using the bolus plus constant infusion method. Both structured (Structured Clinical Interview for the DSM-IV-TR) and unstructured (with a psychiatrist) psychiatric interviews were obtained on all participants. Subjects were excluded if they had taken psychotropic medications or other drugs likely to affect monoamine neurotransmitter function, cerebral physiology or vascular function within 3 wk of scanning (8 wk for fluoxetine). Subjects provided written informed consent after receiving a full explanation of the study procedures and risks, as approved by the National Institute of Mental Health Institutional Review Board.

Scanning was conducted on a GE-Advance scanner in 3D-mode (3D resolution=6 mm full-width at half-maximum). During the scan subjects completed a sensorimotor task (control condition) followed by a gambling task (reward condition). The task consisted of 180 trials, each of average duration 8 s. In the monetary-reward condition subjects received financial

rewards unpredictably, in a pseudo-randomized order with an average of one reward per four trials. In the sensorimotor control condition subjects performed the same task without receiving rewards.

Using a region-of-interest (ROI) approach, mean tissue radioactivity concentrations in the anteroventral striatum, middle caudate and cerebellum from the baseline and reward images were calculated using MEDx software. Mean radioactivity in the reference region (cerebellum; C') was used to control for the effects of free and non-specifically bound [^{11}C]raclopride. The percentage change in [^{11}C]raclopride binding was computed as the difference in BP_{ND} ($C/C'-1$ for each ROI) between baseline and reward images:

$$\Delta BP = \frac{\frac{(C_{reward} - C'_{reward})}{C'_{reward}} - \frac{(C_{baseline} - C'_{baseline})}{C'_{baseline}}}{\frac{(C_{baseline} - C'_{baseline})}{C'_{baseline}}} \times 100$$

The rs1800497 SNP was genotyped using a TaqMan® assay (Life Technologies, USA) and was found to be in Hardy–Weinberg equilibrium in the combined sample (p=1.0), the healthy control sample (p=0.94) and the MDD group (p=0.98). The Illumina GoldenGate platform (Hodgkinson et al., 2008) was used to control for population stratification through the inclusion of 186 ancestry informative markers. To test whether ethnicity predicted D_2 [^{11}C]raclopride binding, we used genetic markers of African and European ancestry as predictors of [^{11}C]raclopride binding in separate regression models. There was no effect of either African or European ancestry on baseline BP_{ND} of the ventral striatum and the middle caudate as well as ΔBP_{ND} of the ventral striatum and the middle caudate (all p values >0.1).

The effect of rs1800497 (A1/A1 *vs.* A1/A2 *vs.* A2/A2) on baseline [^{11}C]raclopride BP_{ND} in the ventral striatum and middle caudate was assessed using a linear regression model controlling for the effects of age, sex and handedness. Because we previously showed that the Ser^{9}Gly SNP in the D_3 receptor gene affects [^{11}C]raclopride BP_{ND} during reward-related DA release (but not baseline [^{11}C]raclopride BP_{ND}; Savitz et al., 2013) we also controlled for Ser^{9}Gly genotype (Ser/Ser *vs.* Ser/Gly *vs.* Gly/Gly) when testing the effect of rs1800497 on the ΔBP_{ND}.

Results

In healthy controls, the A1 allele of the Taq1A SNP was significantly associated with reduced baseline BP_{ND} in both the middle caudate (r^2 explained=0.20, β-weight=0.47, t=2.9, p=0.009) and ventral striatum (r^2 explained=0.20, β-weight=0.46, t=2.6, p=0.016) (Figs. 1 and 2). Conversely, in MDD patients the A1 allele was associated with increased baseline BP_{ND} in the middle caudate (r^2 explained=0.40, β-weight= 0.65, t=2.6, p=0.033) with a trend towards significance in the ventral striatum (r^2 explained=0.28, β-weight= 0.54, t=2.0, p=0.086; Figs. 1 and 2). Severity of depression and self-rated anhedonia were not associated with baseline BP_{ND} in the middle caudate or ventral striatum (all p values>0.1). There were no significant associations between Taq1A genotype and ΔBP_{ND} during reward-associated DA release in the middle caudate or ventral striatum in either the healthy control or the MDD groups (all p values >0.35).

Discussion

Our finding that the TaqA1 allele is associated with reduced $D_{2/3}$ BP_{ND} at baseline in healthy controls replicates the results of two previous PET studies conducted on healthy volunteers reporting reduced availability of the $D_{2/3}$ receptor in the striatum in A1 allele

carriers (Pohjalainen et al., 1998; Jonsson et al., 1999). Our result is also potentially consistent with a more recent study demonstrating an effect of the DRD2 C957T SNP on striatal $D_{2/3}$ BP_{ND} (Hirvonen et al., 2004). The mechanism underlying the contrasting effects of rs1800497 on baseline $D_{2/3}$ receptor binding in MDD patients *vs.* healthy subjects remains unclear, but conceivably may reflect interactions between this SNP (or another SNP in LD with rs1800497) and other genetic or environmental factors associated with MDD. There is a precedent for this kind of gene×diagnosis interaction in the literature.

We previously reported that the T allele of the rs324650 SNP in the muscarinic 2 receptor gene was associated with increased M_2 receptor binding in healthy controls but decreased M_2 receptor binding in patients with bipolar disorder (Cannon et al., 2011). Extant evidence suggests that the short variant of the repeat length polymorphism in the serotonin transporter gene increases the risk for depression when coupled with psychosocial adversity. However, both human and non-human primates who carry the short allele display cognitive and social advantages over long allele homozygotes when raised in a benign environment, possibly because they are more sensitive to positive as well negative stimuli (reviewed in Homberg and Lesch, 2011). Given the Taq1A SNP× psychosocial environment interactions discussed earlier, we raise the possibility that a similar effect may hold for the Taq1A SNP and that this effect may be mediated by differences in D_2 receptor density.

The finding that the Taq1A SNP had a significant effect on baseline $D_{2/3}$ receptor BP_{ND} at baseline but not during reward-related DA release was surprising. Because post-synaptic D_2 receptors outnumber D_2 autoreceptors, the effect of the A1 allele on $[^{11}C]$raclopride binding at rest would predominantly reflect post-synaptic D_2 receptor density (Joyce and Marshall, 1987; Volkow et al., 1996). One possible explanation for the findings is that the Taq1A SNP is associated with decreased coupling of D_2 receptors with post-synaptic effectors, such that the effect of a given level of D_2 stimulation is diminished. Such a functional effect conceivably could account for the differential effects of the Taq1A SNP on DA $D_{2/3}$ receptor binding between depressives and controls.

In controls, the decreased coupling of D_2 receptors with post-synaptic effectors presumably would be compensated by increased baseline tonic DA concentrations, which could account for the decrease in baseline $[^{11}C]$raclopride binding through a competition model (Laruelle, 2000). In depression, in contrast, it might be hypothesized that no compensation occurs, so the decreased tonic DA transmission (i.e. decreased number of DA neurons firing) combines with decreased D_2 signalling efficacy to result in an even greater reduction in DA transmission, as reflected by increased baseline $[^{11}C]$raclopride binding (as reviewed earlier) and the emergence of DA deficiency-driven anhedonia.

This hypothesis appears compatible with the extant data from PET studies of the uptake of $[^{18}F]$fluorodopa ($[^{18}F]$FDOPA), a radiolabelled analogue of the DA precursor L-DOPA. The uptake of $[^{18}F]$FDOPA appears to correlate with the number of DA neurons engaged in firing activity (Howes et al., 2007). Laakso et al. (2005) reported that A1 allele carriers had significantly higher $[^{18}F]$FDOPA uptake in the putamen than A2/A2 homozygotes, a finding that conceivably may reflect the compensatory increase in DA neuron activity that occurs to offset the reduction in D_2 receptor signalling efficacy hypothesized. Although depressed subjects have not been studied with regard to the relationship between the Taq1A polymorphism and $[^{18}F]$FDOPA uptake, it is noteworthy that preliminary studies of DA precursor uptake in depression have shown reductions in $[^{11}C]$DOPA or $[^{18}F]$FDOPA uptake in MDD samples (Agren and Reibring, 1994; Martinot et al., 2001), compatible with a reduction in the number of DA neurons firing. Future studies are needed which assess the differential effect of the Taq1A polymorphism on $[^{18}F]$FDOPA uptake in MDD.

A number of limitations merit comment. The modest sample size may have led to type I or II error, particularly in the smaller MDD group. Large sample sizes are relatively uncommon in PET studies, yet PET has the advantage of allowing a particular molecular target to be assayed directly. It is therefore more likely that true signals can be detected with relatively small sample sizes, potentially explaining our replication of the effect of the Taq1A SNP on $D_{2/3}$ binding in healthy controls.

Our study design does not allow for a rigorous delineation of the potentially divergent effects of the Taq1A SNP on pre-synaptic *vs.* post-synaptic D_2 receptor binding. The D_2 autoreceptor accounts for a proportion of the $[^{11}C]$raclopride signal at baseline and likewise, the post-synaptic D_2 receptor may effect DA release during reward via negative feedback mechanisms.

$[^{11}C]$raclopride binds to both the D_2 and the D_3 receptor and thus we cannot exclude the possibility that DRD3 variants interact with the Taq1A SNP to influence D_2 receptor function. Nevertheless, *in vivo* studies using $[^{11}C]$-(+)-PHNO, a preferential D_3 receptor antagonist, indicate that the D_3 receptor accounts for <10% of the signal in the striatum and caudate at rest (Rabiner et al., 2009; Tziortzi et al., 2011) and in addition, we controlled for our previous finding (in an overlapping sample) that the Ser^9Gly SNP affects $D_{2/3}$ BP_{ND} during the reward task (Savitz et al., 2013) by co-varying for Ser^9Gly genotype in the regression analysis.

In summary, we have replicated prior studies showing that in healthy controls the A1 allele of the TaqA1 SNP is associated with a reduction in $[^{11}C]$raclopride binding at rest. In contrast, however, we found that the A1 allele was associated with increased $[^{11}C]$raclopride BP_{ND} at baseline in depressed subjects with MDD. Our results could conceivably reconcile genetic studies which suggest that the A1 allele is a risk factor for depression and addiction disorders, and some PET studies which report an increase in $D_{2/3}$ receptor binding in MDD and addiction disorders. Nevertheless, we did not observe a significant effect of the TaqA1 SNP on $D_{2/3}$ receptor BP_{ND} during reward-related DA release. These differential effects on basal $D_{2/3}$ receptor BP_{ND} *vs.* phasic DA release conceivably may reflect a greater effect of the TaqA1 SNP on post-synaptic compared to pre-synaptic D_2 receptor function, or a reduction in the coupling of D_2 receptors with post-synaptic effectors, such that the effect of a given level of D_2 stimulation is diminished. Studies involving different experimental designs ultimately are needed to rigorously test these hypotheses.

Acknowledgments

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(a)

(b)
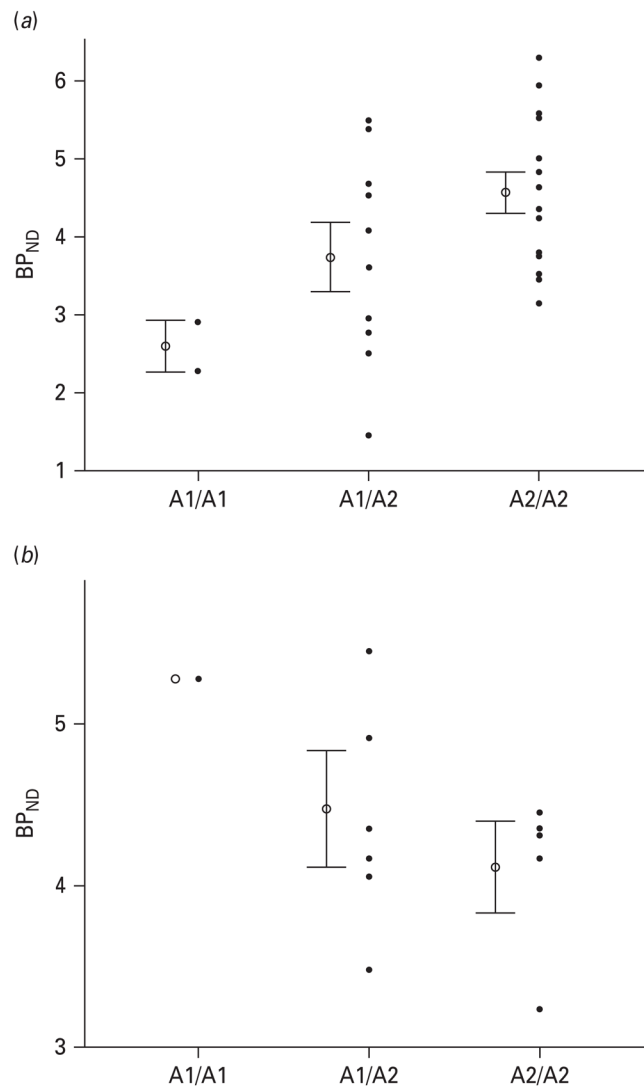
Fig. 1.
(a) Scatterplot of baseline dopamine $D_{2/3}$ receptor binding potential (BP_{ND}) in the ventral striatum of healthy controls stratified according to genotype. The error bars represent the standard error of the mean. The BP_{ND} mean± S.D. for each genotype is as follows: A1/A1=2.6±0.44; A1/A2 =3.8±1.32; A2/A2=4.5±0.98. (b) Scatterplot of baseline $D_{2/3}$ receptor BP_{ND} in the ventral striatum of major depressive disorder patients stratified according to genotype. The error bars represent the standard error of the mean. The BP_{ND} mean± S.D. for each genotype is: A1/A1=5.3±0.0; A1/A2=4.4±0.69; A2/A2=4.1±0.50.
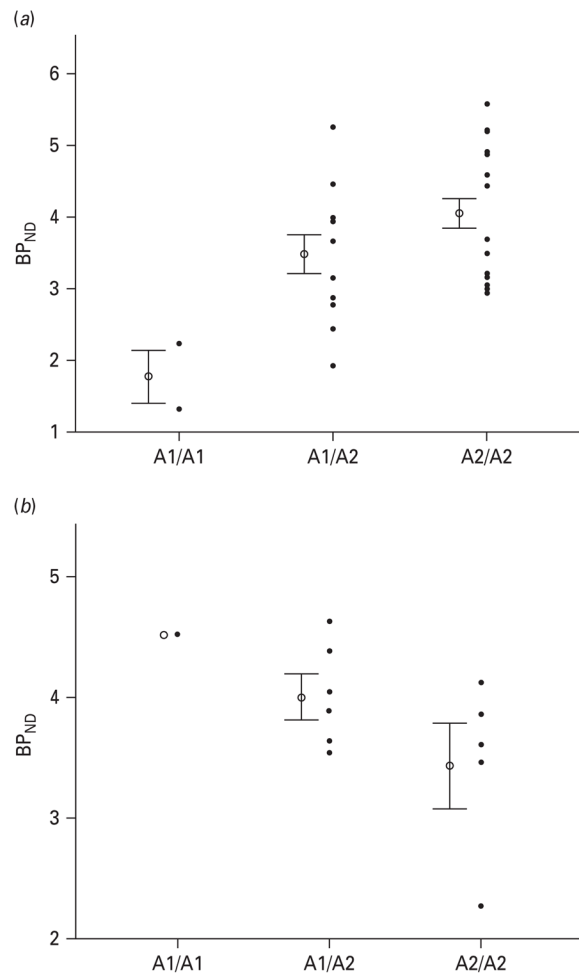
Fig. 2.
(*a*) Scatterplot of baseline dopamine $D_{2/3}$ receptor binding potential (BP_{ND}) in the middle caudate of healthy controls stratified according to genotype. The error bars represent the standard error of the mean. The BP_{ND} mean± S.D. for each genotype is as follows: A1/A1=1.8±0.64; A1/A2 =3.5±1.0; A2/A2=4.0±0.96. (*b*) Scatterplot of baseline $D_{2/3}$ receptor BP_{ND} in the middle caudate of major depressive disorder patients stratified according to genotype. The error bars represent the standard error of the mean. The BP_{ND} mean± S.D. for each genotype is: A1/A1=4.5; A1/A2=4.0±0.42; A2/A2=3.5±0.71.