D₂ Dopamine Receptor Polymorphism and Brain Regional Glucose Metabolism

Ernest P. Noble,^{1*} Louis A. Gottschalk,² James H. Fallon,³ Terry L. Ritchie,¹ and Joseph C. Wu^{2,4}

¹Department of Psychiatry and Biobehavioral Sciences and Brain Research Institute, University of California, Los Angeles, California

²Department of Psychiatry and Human Behavior, University of California, Irvine, California

³Departments of Anatomy and Neurobiology, University of California, Irvine, California

⁴Irvine Brain Imaging Center, University of California, Irvine, California

Positron emission tomography (PET) studies have shown decreased glucose metabolism in brain regions of detoxified alcoholics and cocaine abusers. However, it is not clear whether this decrease is due to chronic drug abuse or a pre-existing condition. Molecular genetic studies have found an association of the D₂ dopamine receptor (DRD2) A1 allele with alcoholism and drug abuse. Moreover, reduced central dopaminergic function has been suggested in subjects who carry the A1 allele (A1⁺) compared with those who do not (A1⁻). In the present study, using ¹⁸F-deoxyglucose, regional glucose metabolism was determined in healthy nonalcohol/nondrug-abusing subjects with the A1⁺ or A1⁻ allele. The mean relative glucose metabolic rate (GMR) was significantly lower in the A1⁺ than the A1⁻ group in many brain regions, including the putamen, nucleus accumbens, frontal and temporal gyri and medial prefrontal, occipito-temporal and orbital cortices. Decreased relative GMR in the A1⁺ group was also found in Broca's area, anterior insula, hippocampus, and substantia nigra. A few brain areas, however, showed increased relative GMR in the A1⁺ group. Since polymorphism of the DRD2 gene is commonly observed in humans, the importance of differentiating A1⁺ and A1⁻ alleles subjects in PET studies is suggested. *Am. J. Med. Genet.* 74:162–166, 1997.

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INTRODUCTION

Brain metabolic abnormalities in alcoholics and cocaine abusers have been identified by PET studies. Wik et al. [1988], using [¹⁴C]glucose, found lower glucose metabolism in frontal, temporal, and parietal cortices and subcortical regions of alcoholics, abstinent for at least 4 weeks, than healthy controls. In alcoholics, abstinent for a minimum of 14 days, Adams et al. [1993] found frontal hypometabolism with 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) as a tracer. FDG studies by Volkow et al. [1994] revealed persistently lower metabolism in the parietal cortex and basal ganglia of alcoholics, 31–60 days after their last alcohol use, when compared to controls. Similarly, in FDG studies of cocaine abusers [Volkow et al., 1992, 1993], hypometabolism in orbito-frontal, cingulate, and prefrontal cortices was found 3–4 months after detoxification. It is not yet determined whether some of these deficits are a consequence of prolonged drug abuse or due to a pre-existing condition.

Recent molecular genetic studies are implicating the D₂ dopamine receptor (DRD2) gene in alcoholism and cocaine abuse. Specifically, the minor allele (A1) of the DRD2 was found to be associated with these drug disorders [for recent reviews, see Neiswanger et al., 1995; Uhl et al., 1995]. Whereas controversy has arisen because some studies have found a lack of significant association of the DRD2 A1 allele with alcoholism, more recent investigations have revealed that the type of controls and alcoholics used are important determinants in this association [Neiswanger et al., 1995; Noble, 1996]. Moreover, the A1 allele phenotype was characterized by reduced brain D₂ dopamine receptor numbers [Noble et al., 1991] and diminished CNS dopaminergic activity [Noble et al., 1994; Berman and Noble, 1995].

To establish whether inherent differences exist in brain glucose metabolism between A1⁺ and A1⁻ subjects, it is necessary to exclude the effects of the alcohol/drug abuse state on this measure. To initiate such a study, brain FDG metabolism was compared in healthy nonalcohol/nondrug-abusing subjects who had either the A1⁺ or the A1⁻ allele of the DRD2 gene.

*Correspondence to: Ernest P. Noble, Ph.D., M.D., Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA 90024-1759.

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The participants were 15 right-handed, randomly-selected Caucasian volunteers with a mean age of 27.3 years ($SE \pm 3.3$). Nine were males and six were females and all were healthy according to history, physical and psychiatric examination, and blood analysis. None of the subjects had a history of alcohol and other drug abuse as determined by interview and administration of a substance abuse questionnaire, or had a family history of psychiatric disorders. Moreover, no subject was on any medication at the time of the study and none had been exposed in the past to any class of neuroleptics. These volunteers gave informed consent and the study followed the guidelines approved by the Human Subjects Institutional Review and Radiation Safety Boards.

TaqI A DRD2 alleles were determined by PCR [Grandy et al., 1993]. The A1/A2 genotype is shown by three fragments of 310 bp, 180 bp, and 130 bp; the A2/A2 genotype is indicated by two fragments of 180 bp and 130 bp; the A1/A1 genotype is revealed by the uncleaved 310 bp fragment.

The subjects, wearing individually molded plastic masks, were positioned in a NeuroECAT scanner (7.6 mm axial resolution [Full Width Half Maximum] in plane and 9.9 mm resolution in the z-dimension) using laser guidance. (The repositioning of subjects during two separate occasions is accurate to within 2 mm [Buchsbaum et al., 1992]). Five mCi 2-deoxy-2-[^{18}F]fluoro-glucose (FDG) was administered to each subject engaged in a visual vigilance task [Neuchterlein et al., 1983]. This task is a continuous performance task (CPT) which deliberately challenges the individual's ability to process information by using rapidly presented blurred images. Approximately 45 minutes after FDG infusion, nine slice images were obtained. Scans were started at the level of 85% of head height (vertex to canthomeatal line, usually 12–14 cm) and stepped downward in intervals of 10 mm. The scans were transformed to glucose metabolic rate (GMR) as described previously [Buchsbaum et al., 1992; Sokoloff, 1984]. The scanner was calibrated on each day with a cylindrical phantom. A dose calibrator served as the standard for gamma counting of blood samples and cylindrical phantom. PET scans were assigned to match the Matsui and Hirano slice (MHS) atlas planes [Matsui and Hirano, 1978] and corresponding Talairach atlas slice planes [Talairach and Tournoux, 1988] by a technician blind to the subject's DRD2 allelic affiliation.

Three brain slices (MHS 6, 8, and 10) were chosen for analysis. Slices MHS 8 and 10 contain the best dopaminergic representations and broad regions of cortical and subcortical areas of interest. As these regions contain a high representation of limbic and associated regions, and since these regions have been implicated in alcohol/drug-seeking behaviors, we hypothesized that they would have important differences between A1⁺ and A1⁻ subjects. Slice MHS 6 was chosen for comparison with the other two slices, since it contains relatively few limbic regions.

The statistical comparisons method was based on normalizing the images for statistical parametric mapping and for placement of stereotaxis regions-of-

interest (ROI) measurements in normalized PET images. The individual slices were normalized by modifying their shape so that they had identical edges. The average PET edge was computed across all individual slices identified as analogous to each slice level in the Matsui and Hirano atlas [1978]. These mean edges were then used to conform each individual PET slice to the average edge contour using radius length adjustment method, normalized for shape. Data for three slices (MHS 6, 8, and 10 which are approximately comparable to Talairach atlas slice 30 mm, 8 mm above the ac-pc line and the slice -4 mm below the ac-pc line, respectively) were obtained.

Previous PET studies have found a large degree of intersubject variability in whole brain GMR values. To make direct comparisons between different subjects involving any specific brain ROI, it is necessary to take into account this potential difference in whole-brain GMR. This was accomplished by dividing GMR values obtained in each subject's ROI by that subject's whole brain mean GMR. This standardized procedure then allows for direct comparison of relative GMR within specific regions across different subjects. Moreover, it allows for more statistically powerful examination of local effects, since global effects are removed.

Between-group *t*-tests were performed on averaged PET images for A1⁺ and A1⁻ allele groups to identify significant differences between these groups. Averaged images differences in relative GMR values were created. The *t*-distribution was then transformed into a *P*-valued image using an approach developed by Friston et al. [1994]. The *P*-valued images were then thresholded ($P < .05$, 2-tailed).

Percent differences for each pixel were displayed only in pixels that were significantly different by *t*-test and by cluster thresholding. The spatial distribution of the profile of *t*-test differences were assessed using image cluster analysis. An estimate of the probability for a given profile of suprathreshold, contiguously connected clusters exceeding a defined probability threshold ($P < .05$) can be assessed if the distribution is known of profiles of activation which are due to chance alone. The probability of a given size contiguous cluster was assessed using this distribution. Forty Monte-Carlo simulations [Good, 1994; Pollack et al., 1994; Widman, 1988] were run ($n = 9$ for A1⁻ allele and $n = 6$ for A1⁺ allele subjects), then 15 subjects (with no repetitions) were randomly selected from our normal control pool ($n = 109$). These 15 subjects were randomly split into two groups containing nine and six individuals. Each group was then averaged separately, a *t*-test was performed, and a corresponding *P*-valued image (*P*-map) was calculated for each of the three MHS levels. This simulation was repeated 40 times so that 40 *P*-maps per MHS level were obtained.

A significance level for the *P*-value was chosen ($P < .05$) and the *P*-maps were thresholded so that only pixels above the significance level were kept. These thresholded *P*-maps were then analyzed for cluster size and their frequency of occurrence. Probability distributions were then obtained for every *P*-map. These probability distributions were then averaged into one prob-

ability distribution function and a corresponding cumulative distribution was calculated.

Based on the simulated cumulative distribution, an estimate of the cluster size versus probability or random occurrence was obtained. The *P*-map calculated from the actual experiment was then analyzed with a threshold which corrected for randomly significant *t*-tests. The significance level ($P < .05$) was chosen from the cumulative distribution and the threshold cluster size was then obtained. All the significant pixel clusters whose size was less than the threshold cluster size were then eliminated. The likelihood of any surviving post-thresholding pixel cluster occurring in selected a priori ROI is $P < .05$ or less. Percent difference images between the two groups of subjects ($A1^+$ and $A1^-$ allele) were calculated for each comparison by subtracting the relative metabolic rate for each pixel of one group from another group and dividing the difference by the value of the first group.

Molecular genetic analysis showed that of the 15 subjects studied, six had the $A1/A2$ genotype ($A1^+$ group) and nine had the $A2/A2$ genotype ($A1^-$ group). There were no significant differences in either age or sex between the $A1^+$ and $A1^-$ groups.

Table I presents the mean relative GMR values in various brain ROI where statistically significant differences were found (in MHS 8 and 10 but not in 6) between $A1^+$ and $A1^-$ groups. Figure 1 depicts graphically significant and nonsignificant regional differences in MHS 6, 8, and 10 following subtraction of mean relative GMR values of the $A1^+$ from $A1^-$ group.

Brains of the $A1^+$ group showed significantly lower

mean relative GMR than those of the $A1^-$ group in a large number of brain regions, including left (L)-Broca's area, and L-middle frontal, L-middle temporal, right (R)-inferior temporal, and R-lateral orbital inferior frontal gyri, as well as striatal regions, including L-caudate, L-putamen, and L-nucleus accumbens. Furthermore, the $A1^+$ group also had significantly lower mean relative GMR in the R-orbital, L-medial prefrontal, and L- and R-lateral occipito-temporal cortices than the $A1^-$ group. Similarly, significant reductions were found in L-anterior insula, L- and R-temporal poles, R-hippocampus, and midbrain in the vicinity of the cerebral peduncle and the substantia nigra. Only in the R-precuneus and its adjacent area was the mean relative GMR significantly higher in the $A1^+$ allele group.

From a neuroanatomical systems perspective, these $A1^+$, $A1^-$ group differences should be interpreted cautiously, pending replication. The lower mean relative GMRs in the $A1^+$ group are found in prefrontal (Broca's area, orbito-frontal cortex), and temporal association cortices (the so-called "ventral" stream of the visual association cortex), and areas of the dorsal striatum (caudate, putamen), ventral striatum (nucleus accumbens), and midbrain at the level of the substantia nigra. These areas are rich to moderately rich in dopamine innervation and dopamine receptors [Smiley et al., 1992; Maeda et al., 1995]. They are also part of the network known as the prefrontal system, which is implicated in the generation of emotions and drives [Stuss and Benson, 1986; Fallon and Loughlin, 1987]. The brain areas showing higher mean relative GMR in

Fig. 1. Subtraction images of $A1^+$ from $A1^-$ allele groups in three Matsui-Hirano slices (MHS 6, 8, 10). The subtraction images were thresholded to display only brain regions significant at $P < .05$, as indicated by the color code.

Regional descriptions: A = R precuneus (31), B = L-anterior insula (16), C = L-middle frontal gyrus (46), D = L-Broca's inferior frontal gyrus (44,45), E = L-caudate, F = L-putamen, G = L-medial prefrontal cortex (32), H = R-orbital cortex (11), I = R-lateral orbital inferior frontal gyrus (47), J = L-temporal pole (38), K = R-temporal pole (38), L = L-middle temporal gyrus (21), M = L-lateral occipito-temporal cortex (37), N = R-lateral occipito-temporal cortex (37), O = R-inferior temporal gyrus (21), P = R-hippocampus, Q = L-nucleus accumbens, R = midbrain/substantia nigra. Numbers in parentheses designate Brodmann areas.

TABLE I. Relationship of Mean Relative Glucose Metabolic Rate (GMR) Between A1⁺ and A1 Allele Subjects

Region of interest	BA	Side	Relative Mean GMR* (±SD)		Significance		Talairach Coordinates		
			A1+	A1−	t	P	x(mm)	y(mm)	z(mm)
Slice 8									
Precuneus	31	R	1.573† (.133)	1.285 (.295)	−2.76	.01	10.2	−63.5	8.0
Anterior insula	16	L	.949 (.179)	1.234 (.239)	3.44	.02	−27.6	16.3	8.0
Middle frontal gyrus	46	L	.940 (.154)	1.272 (.192)	3.38	.02	−34.8	30.6	8.0
Broca's area/inferior frontal gyrus	44,45	L	1.101 (.120)	1.316 (.195)	3.82	.01	−47.1	21.4	8.0
Caudate	—	L	.750 (.171)	.960 (.150)	3.27	.01	−6.1	10.1	8.0
Putamen	—	L	1.118 (.144)	1.330 (.224)	3.22	.01	−18.4	9.1	8.0
Slice 10									
Medial prefrontal cortex	32	L	1.004 (.189)	1.282 (.242)	2.34	.01	−5.0	38.0	−4.0
Orbital cortex	11	R	.971 (.212)	1.255 (.220)	2.52	.01	24.0	22.0	−4.0
Lateral orbital									
Inferior frontal gyrus	47	R	1.232 (.174)	1.450 (.219)	2.02	.02	40.0	25.0	−4.0
Temporal pole	38	L	.941 (.120)	1.111 (.120)	2.73	.01	−45.0	−10.0	−4.0
Temporal pole	38	R	.929 (.151)	1.162 (.153)	2.92	.01	50.0	−7.0	−4.0
Middle temporal gyrus	21	L	.930 (.144)	1.137 (.129)	2.95	.01	−50.0	−30.0	−4.0
Lateral occipito-temporal cortex	37	L	.777 (.118)	.992 (.177)	2.58	.01	−39.0	−43.0	−4.0
Lateral occipito-temporal cortex	37	R	.773 (.118)	.925 (.122)	2.42	.01	45.0	−70.0	−4.0
Inferior temporal gyrus	21	R	1.134 (.166)	1.291 (.123)	2.12	.02	60.0	−19.0	−4.0
Hippocampus	—	R	.846 (.120)	1.033 (.178)	2.22	.01	28.0	−27.0	−4.0
Nucleus accumbens	—	L	.924 (.153)	1.129 (.193)	2.19	.01	−12.0	19.0	−4.0
Midbrain−cerebral peduncle/substantia nigra	—	—	.630 (.094)	.796 (.174)	2.10	.02	15.0	−23.0	−4.0

Stereotaxic coordinates refer to medial lateral position (x) relative to midline (positive = left), anterior-posterior position (y) relative to the anterior commissure (positive = anterior), and height (z) (superior-inferior).

*Micromoles per 100 g brain tissue per minute.

†Only region where A1⁺ is higher than A1⁻ allele.

BA = Brodmann areas.

the A1⁺ group, namely, the precuneus and its adjacent area, are not as densely innervated by dopamine fibers as the prefrontal and striatal system, although they still contain a significant number of dopamine receptors [Joyce et al., 1991]. They are, however, interconnected with dopamine-rich prefrontal cortices and are implicated in language disorders, visuospatial processing, and encoding and retrieval of auditory-verbal memory [Fletcher et al., 1995].

Because brain regional energy metabolism represents primarily metabolic activation of nerve terminals within the region [Schwartz et al., 1976, 1979], the reduced GMR observed in the A1⁺ group may be related, in part, to their diminished dopaminergic activity. Using a dual tracer ([¹⁸F]N-methylspiroperidol and FDG), decreases in D₂ dopamine receptor availability were associated with decreased metabolism in several regions of the frontal lobes of detoxified cocaine abusers [Volkow et al., 1993]. Moreover, as indicated earlier, decreased D₂ dopamine receptor numbers (B_{max}) in the caudate [Noble et al., 1991] was observed in A1⁺ subjects. Specifically, 22% fewer D₂ dopamine receptors were found in A1⁺ allele compared to A1⁻ allele subjects. Interestingly, a 22% lower relative GMR was also found in the caudate of A1⁺ allele subjects of the present study (Table I).

Thus, while the evidence may suggest the involvement of the D₂ dopamine receptor system in the present findings, the contribution of other dopamine receptors and neurotransmitter systems (e.g., GABAergic) to regional metabolism remains unknown. Clearly, additional studies are necessary to validate the present findings. Moreover, the use of specific D₂ dopamine re-

ceptor ligands is indicated in further distinguishing A1⁺ allele from A1⁻ allele subjects.

In conclusion, humans who carry the A1⁺ allele and express lower levels of D₂ dopamine receptors have reduced relative GMR in brain regions closely associated with the prefrontal system and interconnected cortical and subcortical structures that are normally rich in dopamine receptors. Since these structures are known to participate in a variety of complex cognitive and motivational processes and are implicated in several psychiatric disorders, and because the A1⁺ allele is found in about a third of the Caucasian population [Grandy et al., 1989], the present preliminary study suggests the importance of differentiating subjects with the A1⁺ and A1⁻ allele in future cerebral FDG studies.

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