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Dopamine Receptor Binding in the Amygdala Interacts with Gender: A PET Study Using AMPT and [^{18}F]fallypride

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Abstract

Dopaminergic neurotransmission plays an important role in many psychiatric disorders which show sex differences in incidence, clinical course, and treatment outcomes. We examined whether PET studies using [^{18}F]fallypride performed prior to and following Alphamethylparatyrosine (AMPT) administration could be used to estimate sex differences in baseline Dopamine D_2/D_3 receptors (D_2D_3r) occupancy.

Keywords: Dopamine; PET; Humans; [^{18}F]fallypride; Alphamethylparatyrosine challenge

Introduction

Short term AMPT administration produces partial depletion of cerebral Dopamine (DA). Using SPECT or PET and AMPT, it has been possible to assess baseline occupancy of striatal and extrastriatal $DAD_{2/3}$r [1-3]. Baseline occupancy has been interpreted as a measure of baseline DA release. Previous studies have reported sex-related differences in the dopaminergic system. Women have higher striatal [^{18}F]flurodopa uptake, suggestive of greater presynaptic DA synthesis and a lower D2 receptor affinity which reflects their hypothesized higher DA levels [4]. Women also have a greater DA release in the right globus pallidus and inferior frontal gyrus and a greater DA transporter uptake [5-7]. Therefore, compared to men, women seem to have an elevated basal striatal DA levels and increased globus pallidus and inferior frontal gyrus DA levels. Thus, it is important to understand whether there are sex differences in baseline occupancy of $DAD_{2/3}$r in humans in striatal and extrastriatal regions.

Materials and Methods

For a full explanation of methods see Riccardi et al. 2008 [3]. Briefly four females (23 to 38 years, mean age 28) and four males (23 to 32 years, mean age 26) all healthy right-handed non-smoking subjects who had been screened for medical, neurological and psychiatric disease were recruited. None had a history of neither alcohol nor drug abuse. Females were all in the follicular phase. Written informed consent was obtained according to the Institutional Review Board requirements at Vanderbilt University Medical Center. All subjects underwent MRI and PET scans. PET studies were performed using a GE Discovery LS PET scanner with 3-D emission acquisition and transmission attenuation correction. [^{18}F]fallypride PET scans (5.0 mCi, specific activity >2,000 Ci/mmol) were performed under baseline condition and following AMPT administration (72.4 mg/kg p.o. administered in six doses) over 26 h [1-3]. Serial scans were obtained for 3.5 h. To minimize the risk of crystalluria during AMPT administration, subjects were encouraged to drink fluids, intravenous fluids (0.45% saline) were infused until midnight after the second PET study, and sodium bicarbonate (1.2 grams p.o.) was given after the third, fifth, and final AMPT doses. Subjects' urine was tested daily to detect crystal formation. Subjects were asked to rate restlessness, anxiety, speed of thinking, happiness, discomfort and sleepiness on a scale of one to five, and motor neurological examinations were performed before and after AMPT administration.

Blood samples for HVA plasma levels were collected. Serial PET scans were co-registered to each other and to thin section MRI scans and reoriented to the anterior commissure-posterior line with a mutual information rigid body algorithm [8]. Regions of Interest (ROIs), caudate, putamen, ventral striatum, medial thalamus amygdala, temporal cortex, and substantia nigra were delineated on MRI scans and transferred to the co-registered PET scans [9]. Regional DA D_2 receptor Binding Potential (bp) and parametric images of $DAD_{2/3}$r bp were calculated with the reference region

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Table 1: AMPT Induced Increases in Binding Potential (Means and SD).

Region	Baseline bp	Post AMPT bp	% Change	Significance
R Amygdala M	3.94 (0.29)	3.87 (0.25)	-1.80%	0.58
L Amygdala M	3.81 (0.33)	3.82 (0.34)	0.26%	0.95
R Amygdala F	3.30 (0.19)	3.31 (0.13)	0.30%	0.78
L Amygdala F	3.29 (0.24)	3.51 (0.13)	6.70%	0.055

F: Females; M: Males; R: Right; L: Left; AMPT: Alphamethylparatyrosine

method [10-13].

Results and Discussion

Results are shown in Table 1. Analysis of Variance (ANOVA) of the ROI data with treatment status (pre/post AMPT), region, sex (female/male) and laterality (left/right) as factors revealed significant effects only in the amygdala in the right (F=9.403, P=0.002) and left (F=3.486, P=0.05) sides. Post hoc specifically comparisons (LSD method) revealed that at baseline prior to AMPT administration in the right amygdala, the bp of males was significantly ($p<0.005$) greater than for females. Following AMPT administration, males again had greater bp compared to females in both right (p=0.002) and the left (p=0.005). Differences in the mean level of corresponding measurements on status were tested by using a matched pair's t test. P values equal to 0.05 were interpreted as statistically significant. An increase in bp after AMPT treatment was observed only in females for the left amygdala with a percentage of change of 6.7%. This was significant for a p=0.055 (Table 2). When left and right sided amygdala was combined together, the percentage of change for females was 3.64%. This was significant for a p=0.026. No increase in bp was observed in our previous analysis of these data in the amygdala when male and female were grouped together (___). None of the subjects required treatment for side effects of AMPT. All subjects were mildly to moderately somnolent and had mild slowing of rapid repetitive movements. All subjects experienced some slowing of mentation. Plasma HVA levels were not statistically different between female and male subjects. This study demonstrated a sex differences in bp in the amygdala with males showing at baseline significantly higher $D_{2/3}$ receptor availability in both the right and left amygdala, reflecting a reduced synaptic dopamine level in these areas. This difference is not due to a difference in volume [14]. Dopaminergic depletion by AMPT unmasked an inherently sex-specific direction of modulation in females showing an endogenous asymmetry as the left amygdala has a higher concentration of DA than the right. Both in humans and animals, the amygdala has been shown to be functionally asymmetrical and significantly modulated by DA [15,16]. Moreover, the DA D_2 receptor antagonist sultopride and the DA agonist levodopa both attenuate amygdala activation in healthy subjects [17,18]. DA in the amygdala is an important component implicated in emotional responses, learning, and drug abuse [19-21]. Both in animals and humans, male and females, respond differently to stress, learning and drug abuse suggesting a sex-specific response in the amygdala [22-25]. Similarly, differences have been demonstrated between men and women in neural activity during receptive and expressive emotion. Using fMRI and a mood-induced paradigm, Schneider, found increased activity in the right amygdala for men, but not women during expression of negative affect [26]. Cahill et al. [27], among others, reported that activity in the left hemisphere amygdala relates significantly to long-term subsequent memory in women; whereas, activity in the right hemisphere amygdala relates significantly to long-term subsequent memory in men. Using an

Table 2: AMPT induce increases in right and left Amygdala Binding Potential (Means and SD).

Group	Mean (SD)	Group	Mean (SD)
Males Baseline bp	3.89 (0.30)	Females Baseline bp	3.30 (0.22)
Males Post AMPT bp	3.85 (0.28)	Females Post AMPT bp	3.42 (0.12)
% Change	-1.03%	% Change	3.64%
Males Baseline	Significance	Males Post AMPT	Significance
Females Baseline	0.005	Females Post AMPT	0.026

emotional challenge as the stimulus in another [^{18}F]fallypride PET study, Vainer and colleagues [28], found sex and hemisphere-dependent alterations of dopaminergic tone in the amygdala, with males exhibiting right-sided and females exhibiting left-sided biases of [^{19}F]fallypride binding linked to subsequent memory for the emotional stimuli. Sex by hemisphere interactions exist even concerning the functional activity of the human amygdala during resting conditions [29,30], a fact which strongly suggests that such interactions must be accounted for in essentially all studies of human amygdala function. There have been a variety of studies in humans supporting the role of the amygdala in neuropsychiatric illnesses. For instance, an elevated binding to D_2 receptors was observed in the amygdala in a post-mortem sample of a depressed patient [31]. Furthermore, a type of alcoholism, characterized by late-onset, social dependency and anxiety (i.e. Type 1) has been suggested to be associated with an underlying dopaminergic deficit in the amygdala in a sample of seven males and two females [???]. The present findings may suggest that the DA in the amygdala is involved in a sex-specific manner in neuropsychiatric disorders in which a dysregulation of amygdala activation has been postulated [32-34]. Further studies with more subjects are needed to confirm these findings.

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References

1. Laruelle M, D'Souza CD, Baldwin RM, Abi-Dargham A, Kanes SJ, Fingado CL, et al. Imaging D2 receptor occupancy by endogenous dopamine in humans. Neuropsychopharmacology. 1997;17(3):162-74.
2. Verhoeff NP, Kapur S, Hussey D, Lee M, Christensen B, C Psych, et al. A simple method to measure baseline occupancy of neostriatal dopamine D2 receptors by dopamine in vivo in healthy subjects. Neuropsychopharmacology. 2001;25(2):213-23.
3. Riccardi P, Baldwin R, Salomon R, Anderson S, Ansari MS, Li R, et al. Estimation of baseline dopamine D2 receptor occupancy in striatum and extrastriatal regions in humans with positron emission tomography with [18F] fallypride. Biol Psychiatry. 2008;63(2):241-4.
4. Laakso A, Vilkman H, Bergman J, Haaparanta M, Solin O, Syvalahti E, et al. Sex differences in striatal presynaptic dopamine synthesis capacity in healthy subjects. Biol Psychiatry. 2002;52(7):759-63.

5. Riccardi P, Zald D, Li R, Park S, Ansari MS, Dawant B, et al. Sex differences in amphetamine-induced displacement of [(18)F] fallypride in striatal and extrastriatal regions: a PET study. Am J Psychiatry. 2006;163(9):1639-41.
6. Lavalaye J, Booij J, Renemann L, Habraken JB, van Royen EA. Effect of age and gender on dopamine transporter imaging with [123]FP-CIT SPET in healthy volunteers. Eur J Nucl Med. 2000;27(7):867-9.
7. Mozley LH, Gur RC, Mozley PD, Gur RE. Striatal dopamine transporters and cognitive functioning in healthy men and women. Am J Psychiatry. 2001;158:1492-9.
8. Pluim JPW, Maintz JBA, Viergever MA. Mutual information matching in multiresolution context. Image and Vision Computing. 2001;19:45-52.
9. Kessler RM, Ansari MS, Riccardi P, Li R, Jayathilake R, Dawant B, et al. Occupancy of striatal and extrastriatal dopamine D2 receptors by clozapine and quetiapine. Neuropsychopharmacology. 2006;31:1991-2001.
10. Lammertsma AA, Bench CJ, Hume SP, Osman S, Gunn K, Brooks DJ, et al. Comparison of methods for analysis of clinical [11C] raclopride studies. J Cereb Blood Flow Metab. 1996;16(1):42-52.
11. Kessler RM, Mason NS, Jones C, Ansari MS, Manning RF, Price RR. [18F] N-allyl-5-fluoroprorlepidepride (fallypride): Radiation dosimetry, quantification of striatal and extrastriatal dopamine receptors in man. Neuro Image. 2000;11:32.
12. Grunder G, Landvogt C, Vernaleken I, Buchholz HG, Ondracek J, Siessmeier T, et al. The striatal and extrastriatal D2/D3 receptor-binding profile of clozapine in patients with schizophrenia. Neuropsychopharmacology. 2006;31(5):1027-35.
13. Siessmeier T, Zhou Y, Buchholz HG, Landvogt C, Vernaleken I, Piel M, et al. Parametric mapping of binding in human brain of D2 receptor ligands of different affinities. J Nucl Med. 2005;46(6):964-72.
14. Brabec J, Rulseh A, Hoyt B, Vizek M, Horinek D, Hort, J et al. Volumetry of the human amygdala – An anatomical study. Psychiatry Res. 2010;182(1):67-72.
15. Kienast T, Hariri AR, Schlagenhauf F, Wrase J, Sterzer P, Buchholz HG, et al. Dopamine in amygdala gates limbic processing of aversive stimuli in humans. Nat Neurosci. 2008;11(12):1381-2.
16. Tessitore A, Hariri AR, Fera F, Smith WG, Chase TN, Hyde TM, et al. Dopamine modulates the response of the human amygdala: a study in Parkinson's disease. J Neurosci. 2002;22(20):9099-103.
17. Delaveau P, Salgado-Pineda P, Micallef-Roll J, Blin O. Amygdala activation modulated by levodopa during emotional recognition processing in healthy volunteers. A double-blind, placebo-controlled study. J Clin Psychopharmacol. 2007;27(6):692-7.
18. Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, et al. Effects of dopaminergic and serotonergic manipulation on emotional processing: A pharmacological fMRI study. Neuroimage. 2005;27(4):991-1001.
19. Rosenkranz JA, Grace AA. Cellular mechanisms of infralimbic and prelimbic prefrontal cortical inhibition and dopaminergic modulation of basolateral amygdala neurons *in vivo*. J Neurosci. 2002;22(1):324-37.
20. Rosenkranz JA, Grace AA. Dopamine-mediated modulation of odour-evoked amygdala potentials during pavlovian conditioning. Nature. 2002;417(6886):282-7.
21. Tye KM, Tye LD, Cone JJ, Hekkelman EF, Janak PH, Bonci A. Methylphenidate facilitates learning-induced amygdala plasticity. Nat Neurosci. 2010;13(4):475-81.
22. Tupala E, Hall H, Bergstrom K, Sarkioja T, Rasanen P, Mantere T, et al. Dopamine D(2)/D(3)-receptor and transporter densities in nucleus accumbens and amygdala of type 1 and 2 alcoholics. Mol Psychiatry. 2001;6(3):261-7.
23. Sullivan RM, Dufresne MM, Waldron J. Lateralized sex differences in stress-induced dopamine release in the rat. Neuroreport. 2009;20(3):229-32.
24. Kilts CD, Gross RE, Ely TD, Drexler KP. The neural correlates of cue-induced craving in cocaine-dependent women. Am J Psychiatry. 2004;161(2):233-41.
25. Koob GF. The neurobiology of addiction: a neuroadaptational view relevant for diagnosis. Addiction. 2006;101 Suppl 1:23-30.
26. Schneider F, Habel U, KIessler C, Salloum JB, Posse S. Gender differences in regional cerebral activity during sadness. Hum Brain Mapp. 2000;9(4):226-38.
27. Cahill L, Uncapher M. Kilpatrick L, Alkire MT, Turner J. Sex-related hemispheric lateralization of amygdala function in emotionally influenced memory: an fMRI investigation. Learn Mem. 2004;11(3):261-6.
28. Vainer Y, Mandelkern MA, Cahill L. Dopaminergic amygdala activity and emotional memory in men and women. Poster Presentation. Society for Neuroscience Annual Conference 2006.
29. Kilpatrick LA, Zald DH, Pardo JV, Cahill LF. Sex-related differences in amygdala functional connectivity during resting conditions. Neuroimage. 2006;30(2):452-61.
30. Savic I, Lindstrom P. PET and MRI show differences in cerebral asymmetry and functional connectivity between homo- and heterosexual subjects. Proc Natl Acad Sci USA. 2008:105(27):9403-8.
31. Klimek V, Schenck JE, Han H, Stockmeier CA, Ordway GA. Dopaminergic abnormalities in amygdaloid nuclei in major depression: a postmortem study. Biol Psychiatry. 2002;52(7):740-8.
32. Taylor SF, Liberzon I, Decker LR, Koeppe RA. Functional anatomic study of emotion in schizophrenia. Schizophr Res. 2002;58(2-3):159-72.
33. Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry. 2001;50(9):651-8.
34. Sibille E, Wang Y, Joeyen-Waldorf J, Gaiteri C, Surget A, Oh S, et al. A molecular signature of depression in the amygdala. Am J Psychiatry. 2009;166(9):1011-24.