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_{2/3r} [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]fluorodopa 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_{2/3r} 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_{2/3} receptor Binding Potential (bp) and parametric images of DAD_{2/3r} bp were calculated with the reference region.
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=0.03) 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 in the right 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 (Table 2). 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 D2 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 D2 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 emotional challenge as the stimulus in another [18F]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 [18F]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 D2 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 I) has been suggested to be associated with an underlying dopaminergic deficit in the amygdala in a sample of seven males and two females [32-34]. 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


