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Effects of catecholamine depletion on D_2 receptor binding, mood, and attentiveness in humans: a replication study

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Abstract

The effect of catecholamine depletion, achieved by per-oral administration of 5250 mg α-methyl-*para*-tyrosine (AMPT) given in the 29 h prior to [^{11}C]raclopride positron emission tomography (PET) was studied on measures of dopamine (DA) release, mood, and attention. Neostriatal DA levels in vivo were estimated by comparing the neostriatal DA D_2 receptor binding potential (D_2RBP) before and after catecholamine depletion using PET and the radiotracer [^{11}C]raclopride. Six healthy subjects completed the protocol. The AMPT treatment increased D_2RBP significantly by 13.3 ± 5.9% (average ± standard deviation) and decreased plasma levels of the DA metabolite homovanillic acid (HVA) by 62 ± 17%, and levels of the norepinephrine (NE) metabolite 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) by 66 ± 5%. Catecholamine depletion resulted in decreased happiness, euphoria, energy, talkativeness, vigor, and attentiveness, and in increased sleepiness, fatigue, sedation, and eye blink rate (EBR). These changes were not correlated with the D_2RBP increments. The results of this study are overall consistent with previous findings by our group using the same methodology in a different cohort of six healthy subjects.

Keywords: Dopamine; Dopamine D_2 receptors; [^{11}C]raclopride; Positron emission tomography; α-Methyl-*para*-tyrosine; In vivo binding

1. Introduction

We have recently developed a protocol to estimate neostriatal dopamine (DA) levels with positron emission tomography (PET) and [^{11}C]raclopride (Verhoeff et al., 2001). However, the sample size in our previous study was limited. Therefore, the present replication study reports data obtained from an additional cohort of healthy subjects.

In our previous PET study, significant α-methyl-*para*-tyrosine (AMPT)-associated changes were observed in subjective scores for happiness and sleepiness (Verhoeff et al., 2001). Moreover, increases in neostriatal DA D_2 receptor binding potential (D_2RBP) correlated with decreases in attentiveness and with increases in errors of commission from the Conners' Continuous Performance Test (CPT). These data were in concordance with both a previous SPECT study (Laruelle et al., 1997) and with the hypothesized role of the dopaminergic system in selective attention (Cohen and Servan-Schreiber, 1992; Cornblatt and Keilp, 1994; Servan-Schreiber et al. 1998a,b). However, because of the small sample size in our original study ($n = 6$), we believed that an imperative step in establishing the validity of these effects was to test them in a different cohort ($n = 6$).

As alterations in dopaminergic transmission may be involved in various other cognitive functions, such as

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visuospatial working memory (Park and Holzman, 1992; Williams and Goldman-Rakic, 1995; Fleming et al., 1997), and oral word production (Bilder et al., 1992; Szeszko et al., 1999), these functions were tested in the healthy subjects at baseline and at different stages of AMPT-induced DA depletion. A finger-tapping task was included in order to control for possible effects of DA depletion on motor speed. Since self-reported sleepiness during AMPT depletion has been reported to be a good predictor of poor performance on cognitive tests (McCann et al., 1992), not only subjective ratings but also objective ratings were obtained for sedation during each series of cognitive tests. Also, some cognitive tests were incorporated that were not expected to change with DA depletion such as reading ability, abstract reasoning, and knowledge of general information so as to verify the specificity of DA depletion on the hypothesized cognitive domains (i.e., rule out a general effect of DA depletion on all cognition).

2. Materials and methods

2.1. Human subjects

The study was approved by the Human Subjects Review Committee of the University of Toronto and has been carried out in accordance with the Declaration of Helsinki for human subjects of 1975. Five women and one man, age 27 ± 8 years (all values in this article are expressed as mean ± standard deviation) and all right-handed, completed the study. Inclusion and exclusion criteria were the same as for our original study (Verhoeff et al., 2001).

2.2. Catecholamine depletion regimen

The catecholamine depletion regimen in these subjects has been described previously (Verhoeff et al., 2002).

2.3. Clinical monitoring

Subjects were evaluated five times using clinical rating scales for adverse effects and mood states pre-AMPT (on Day 1 and on Day 2) and post-AMPT (cumulative oral doses of 750 mg on Day 2, and 3750 and 5250 mg on Day 3). The presence of adverse effects such as parkinsonian symptoms, acute dystonias, and abnormal involuntary movements was monitored using the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al., 1980). Effects on eye blink rate (EBR) were assessed by counting the number of blinks during a 2.5-min period (Taylor et al., 1999). EBR was calculated as mean number of blinks per minute. The observer was seated in front of the subject, and EBR and abnormal involuntary movements were monitored simultaneously. Attempts were made not to stare directly at the subject's eyes. Effects on handwriting area were analyzed in the subjects using a planimetric computerized version of the Haase Neuroleptic Threshold Test (HNTT; Haase and Janssen, 1985). All subjects rated 19 subjective feelings on a continuous visual analog scale (VAS; Bond and Lader, 1974) ranging from 0% (*not at all*) to 100% (*most ever*). Subjective feelings were also rated using the ordinal Profile of Mood States (POMS; McNair et al., 1981). In addition, subjects rated depressive symptoms using the Beck Depression Inventory, Short Form (BDI; Beck et al., 1974).

The subjects performed the following cognitive tests pre-AMPT (Day 1), post 1500 mg AMPT (Day 2) and post 3750 mg AMPT (Day 3): Conners' Continuous Performance Test (CPT; Conners, 1995), Logan's Stop Signal Task (SST; five subjects only; Logan et al., 1984; Solanto et al., 2001), Stroop Color–Word Test (SCWT; all six subjects; Stroop, 1935), Oculo-Motor Delayed Response Test (OMDR; Hershey et al., 1998), Controlled Oral Word Association Test (COWAT; Benton and Hamsher, 1978), Category Fluency Animal Naming Test (CFANT; Baldo et al., 2001), Finger Tapping Test (FTT; Reitan and Wolfson, 1985), Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) Matrix Reasoning and Information subtests (Wechsler, 1997a,b), and Wide Range Achievement Test 3 reading subtest (WRAT3; Wilkinson, 1993). Subjects were rated during these tests regarding level of sedation using the Observer's Assessment of Alertness/Sedation Scale (OAASS; Chernik et al., 1990).

2.4. Plasma analyses

Plasma homovanillic acid (HVA), 3-methoxy-4-hydroxyphenethyleneglycol (MHPG), and prolactin samples were collected and analyzed in these subjects as described previously (Verhoeff et al., 2002).

2.5. [^{11}C]raclopride PET data acquisition and analysis

The [^{11}C]raclopride PET data were acquired and analyzed in these subjects as described previously (Verhoeff et al., 2002). The neostriatal DA D_2 receptor binding potential (D_2RBP), the product of the total D_2R density (B_{max}), and the affinity ($1/K_d$) of [^{11}C]raclopride for D_2R were calculated using the simplified three-parameter reference tissue model (SRTM; Lammertsma and Hume, 1996). Since DA competes with [^{11}C]raclopride binding, the fractional D_2RBP increase ($D_2RBP_{shift}=(D_2RBP_{depleted} - D_2RBP_{baseline})/D_2RBP_{baseline}$) is linearly proportional to the baseline DA level, provided DA depletion does not change D_2R density and/or affinity (Verhoeff et al., 2001, 2002).

2.6. Statistical analyses

Data were screened for univariate statistical violation by testing for skewness, kurtosis, and outliers, and for inhomogeneity of variance (Tabachnick and Fidell, 1996). AMPT effects on PET measurements were assessed by two-tailed

paired Student's t test if these criteria for a normal distribution and homogeneity of variance were met and by Wilcoxon's signed ranks test if these criteria were not met. Similarly, AMPT effects on clinical ratings and plasma levels were assessed by repeated-measures analysis of variance (ANOVA) if the criteria were met and by Friedman's test if the criteria were not met. Correlations between PET data and clinical parameters that changed significantly with AMPT treatment were tested using Pearson's product–moment correlation coefficient (r) if the criteria were met and using Spearman's rank correlation coefficient (ρ) if the criteria were not met. All tests were two-tailed and probability values of .05 were used as the significance level. As in the previous reports (Verhoeff et al., 2001, 2002), in these exploratory analyses, no corrections for multiple comparisons were applied. Statistical analyses were performed with SPSS for Windows, release 10.0.0 (SPSS, Chicago, IL, 1999).

3. Results

3.1. [^{11}C]raclopride PET

The D_2RBP was 3.18 ± 0.34 pre-AMPT and increased significantly to 3.59 ± 0.30 post-AMPT (paired t test: t = − 5.754, df = 5, P=.002). The D_2RBP_{shift} was 0.133 ±0.059. These results, as well as the effects of AMPT treatment on the SRTM parameters R_1 and k_2, have been reported previously (Verhoeff et al., 2002).

3.2. Plasma levels

Treatment with AMPT resulted in significant decreases in plasma levels of the DA metabolite homovanillic acid (HVA) by 62 ± 17% and of the norepinephrine (NE) metabolite 3-methoxy-4-hydroxyphenethyleneglycol (MHPG) by 66 ± 5%, and in significant increases in prolactin levels by 369 ± 89%. These results have been reported previously (Verhoeff et al., 2002). Post-AMPT, MHPG levels were inversely correlated with D_2RBP (r = − .837, P=.038). Age was correlated to prolactin levels post-AMPT (ρ=.943, P=.005) and to AMPT-induced prolactin level increase (ρ=.829, P=.042).

3.3. Clinical effects of AMPT

Only very mild Parkinsonian symptoms and akathisia were induced by AMPT in two of our subjects. No acute dystonias or abnormal involuntary movements were observed.

Effects of AMPT on EBR and on the HNTT are shown in Table 1. EBR increased significantly on AMPT. Pre-AMPT, EBR was inversely correlated with MHPG levels (r = − .825, P=.043). Post-AMPT, EBR was correlated with D_2RBP (r=.852, P=.031) and showed a trend for an inverse correlation with MHPG levels (r = − .745, P=.089). EBR increase on AMPT was not correlated with any imaging, plasma, or mood measures. No significant effects on the HNTT were observed.

Table 1
Effects of AMPT on EBR, on handwriting area, and on subjective mood ratings

Test item	Baseline	AMPT (750 mg)	AMPT (3750 mg)	AMPT (4500 mg)	Significance of change[a]
Motor scores					
EBR	11 ± 7	13 ± 10	20 ± 9	26 ± 10	.002
Handwriting area (% baseline)	100	99 ± 10	106 ± 12	104 ± 15	.597
VAS items					
Happy	73 ± 14	66 ± 24	55 ± 18	44 ± 19	.006
High	17 ± 22	8 ± 16	6 ± 15	6 ± 15	.014^
Energetic	53 ± 14	44 ± 26	17 ± 10	22 ± 38	.015^
Talkative	61 ± 22	49 ± 27	43 ± 24	32 ± 24	.024
Sleepy	49 ± 23	53 ± 20	76 ± 34	79 ± 21	.024
Restless	11 ± 20	7 ± 16	30 ± 35	19 ± 18	.058^
Hungry	13 ± 20	4 ± 10	8 ± 20	4 ± 10	.066^
Drowsy	40 ± 21	44 ± 27	70 ± 36	67 ± 28	.070
POMS dimensions					
Vigor	11.7 ± 5.2	8.0 ± 4.6	3.3 ± 1.8	3.2 ± 5.0	.002
Fatigue	6.5 ± 3.5	5.3 ± 4.1	8.3 ± 4.2	10.3 ± 2.3	.038

Levels of significance of change in EBR, handwriting (HNTT), visual analogue scale (VAS) and profile of mood state (POMS) scores over four cumulative oral doses of AMPT: 0 (average of two measurements per subject), 750, 3750, and 4500 mg (one measurement each per subject). Values expressed as mean ± standard deviation.

[a] P values from repeated-measures ANOVA (if data met criteria for normal distribution) are not marked, whereas P values from Friedman's test (if data did not meet criteria for normal distribution) are marked with ^.

Effects of AMPT on the VAS and POMS are shown in Table 1. On AMPT, VAS scores for happiness, feeling high, feeling energetic, and talkativeness, and POMS scores for vigor were significantly decreased, whereas VAS scores for sleepiness and POMS scores for fatigue were significantly increased. Trends for increases in VAS scores for restlessness and drowsiness and for a decrease in feeling hungry were also observed. No significant changes on AMPT were observed for the other VAS item scores, in order of decreasing significance: tired, calm, mania, nervous, angry, mellow, fearful, sad, irritable, anxious, and depressed. Also, no significant changes on AMPT were observed for the other POMS dimension scores, in order of decreasing significance: anger, confusion, tension, and depression. Pre-AMPT, happiness scores were correlated with HVA levels (r=.857, P=.029). Decrease in happiness scores on AMPT was correlated to percentage MHPG decrease (r=.931, P=.007) but not to percentage HVA decrease or to D_2RBP_{shift}. Post-AMPT, talkativeness scores were inversely correlated with EBR (r = − .837, P=.038). Decrease in talkativeness scores on AMPT was correlated with AMPT levels (r=.892, P=.017) and with decrease in feeling high (ρ=.971, P=.001). BDI scores were very low and did not

change with AMPT treatment. Post-AMPT, vigor scores were correlated with age (r=.925, P=.008).

Effects of AMPT on cognitive test performance are shown in Table 2. The OAASS overall scores decreased significantly on AMPT, indicating greater sedation on AMPT. The AMPT-induced decrease in OAASS overall scores was correlated with the increase in VAS sleepiness scores (ρ=.926, P=.008).

Significant effects of AMPT on many CPT items were observed: Attentiveness (d') and number of hits decreased whereas risk taking, overall index, number of omissions, and hit response time standard error increased. No significant changes on AMPT were observed for the other CPT items, in order of decreasing significance: number of commissions, hit response time change over interstimulus intervals, variability of standard errors, hit response time, hit standard error change over interstimulus intervals, hit response time block change, and hit standard error block change. Pre-AMPT, attentiveness scores were correlated with prolactin levels (ρ=.928, P=.008), and OAASS overall scores were correlated with number of hits (ρ=1.000, P<.001) and were inversely correlated with number of omissions (ρ=1.000, P<.001). Post-AMPT, attentiveness scores were correlated with VAS scores for feeling energetic (ρ=.845, P=.034) and with OAASS overall scores (ρ=.833, P=.039), whereas D_2RBP was correlated to risk taking (ρ=.841, P=.036) and number of omissions (ρ=.812, P=.050), and was inversely correlated to number of hits (ρ=−.812, P=.050). The AMPT-induced increase in overall index scores was correlated with age (r=.889, P=.018) and with increase in EBR (r=.822, P=.045). The AMPT-induced increase in hit response time standard error scores was correlated with the decrease in feeling high (ρ=−.812, P=.050).

A trend for an increased response time on AMPT was observed for the SST. On the SCWT, the response time for matched words decreased significantly, whereas a trend for decreased response time was observed for colored X's. No significant effects on Stroop interference were observed. Post-AMPT, response times for matched words were inversely correlated to D_2RBP (r=−.903, P=.014) and correlated to MHPG levels (r=.857, P=.029). The decrease in response times for matched words with AMPT treatment was inversely correlated with the decrease in POMS vigor scores (r=−.838, P=.037). No significant AMPT-induced changes were observed for scores from the OMDR, COWAT, CFANT, FTT, WAIS-III Information or Matrix Reasoning modules, or WRAT3 scores, except for a decrease in word production during the 45–60-s interval of the COWAT.

Table 2
Effects of AMPT on cognitive test performance

Cognitive test item	Baseline	AMPT (1500 mg)	AMPT (3750 mg)	Significance of change[a]
Sedation				
OAASS total score	4.8±0.4	4.0±0.6	3.7±0.8	.010^
Conners' CPT				
Attentiveness (d')	3.81±0.81	2.70±1.11	2.46±1.25	<.001
Risk taking	0.04±0.01	0.13±0.10	0.30±0.28	.002^
Overall index	2.59±4.14	8.36±6.19	10.73±7.16	.005
Number of hits	323±0	321±2	313±11	.006^
Number of omissions	1.17±0.41	3.33±1.51	11.00±11.08	.006^
Hit response time standard error	4.82±0.93	6.12±2.37	7.49±2.74	.019
Logan's SST (n=5)				
Logan's SSRT (for X)	174.7±25.2	181.8±28.5	227.7±44.4	.089
SCWT				
Word (match)	16.0±5.2	13.2±2.7	12.5±2.2	.032
Color (XXXX)	15.4±2.8	13.9±2.0	13.9±1.9	.071
COWAT				
FAS words 45–60 s	8±3	10±3	7±3	.012

Levels of significance of change in plasma levels over three cumulative oral doses of AMPT: 0 (average of two measurements per subject), 1500, and 4500 (one measurement each per subject). Values expressed as mean± standard deviation.

[a] P values from repeated-measures ANOVA (if data met criteria for normal distribution) are not marked, whereas P values from Friedman's test (if data did not meet criteria for normal distribution) are marked with ^.

4. Discussion

4.1. [^{11}C]raclopride PET

AMPT-induced DA depletion resulted in a significant increase in D_2RBP of 13.3±5.9% (Verhoeff et al., 2002). This is consistent with the D_2RBP increase observed previously by our group (Verhoeff et al., 2001).

4.2. Plasma levels

The plasma levels of AMPT, HVA, MHPG, and prolactin in this study have been discussed elsewhere (Verhoeff et al., 2002) and were consistent with the plasma levels observed in our previous study (Verhoeff et al., 2001).

4.3. Clinical effects of AMPT

The EBR increase on AMPT was contrary to our expectations, as previous data suggested that EBR usually decreases with reductions in dopaminergic transmission (Taylor et al., 1999). Since the DA depletion in our paradigm was only partial and no clinically significant extrapyramidal adverse effects and no changes in the HNTT were observed, it may be that a relative imbalance in D_1R versus D_2R stimulation induced the EBR increase. With more profound DA depletion, EBR decrease would be expected. Thus, there may be an inverted-U relationship between catecholamine levels and

EBR. The inverse correlations between EBR and MHPG levels pre- and post-AMPT suggest that besides dopaminergic also norepinephrinergic transmission may play a role in EBR. It seems unlikely that the EBR increase was due to increased sedation with increased difficulty to keep the eyes open, as it was not correlated with any of the increases in subjective or objective sedation scores.

The significant decreases in VAS happiness and POMS vigor scores and the increases in VAS sleepiness and POMS fatigue scores on AMPT in our study have also been observed in healthy subjects by others (McCann et al., 1993; Laruelle et al., 1997) and in our previous study (Verhoeff et al., 2001). The fact that the decrease in happiness was highly and significantly correlated to MHPG decrease but not to HVA decrease or D_2RBP_{shift}, confirming the result in our previous study (Verhoeff et al., 2001), suggests a larger role for NE depletion than for DA depletion. The AMPT-induced decrease in feeling high suggests a continuum in which the increases in euphoria related to increased catecholamine release induced by amphetamine (Drevets et al., 2001) or methylphenidate (Volkow et al., 1999) form the opposite of the spectrum.

The lack of AMPT-induced changes in depression scores on VAS, POMS, and BDI is compatible with previous reports that healthy subjects do not experience significant depressive symptoms on AMPT (McCann et al., 1993; Zimmermann et al., 1996; Salomon et al., 1997; Laruelle et al., 1997; Abi-Dargham et al., 2000; Fujita et al., 2000; Verhoeff et al., 2001).

The reduction in performance on a broad range of CPT items on AMPT in the present study was even more pronounced than in the previous study (Verhoeff et al., 2001), indicating that this is a reliable finding. The most pronounced decrease was observed for attentiveness (d'), the CPT measure for selective attentiveness. These data are in accordance with data showing an improvement in selective attention in healthy subjects after oral D-amphetamine administration (Servan-Schreiber et al., 1998b). Collectively, these data suggest that increasing dopaminergic transmission improves, and decreasing dopaminergic transmission worsens, selective attention in healthy subjects. Whereas D-amphetamine induced a speeding of reaction time overall and an improvement of accuracy at fast reaction times (Servan-Schreiber et al., 1998b), AMPT in our study did not affect reaction time and reduced accuracy mainly by increased risk taking and errors of omission. This is in contrast with our previous study, in which AMPT reduced accuracy mainly by increasing errors of commission (Verhoeff et al., 2001). The lack of any AMPT effect on the motor aspects of the reaction time is compatible with the fact that we did not detect any significant changes in ESRS, HNTT, and FTT scores. This lack of motor changes on AMPT is consistent with the findings in our previous study (Verhoeff et al., 2001). In contrast to the observation by McCann et al. (1992) that subjective ratings of sedation in healthy subjects on AMPT were significantly correlated with their performance on cognitive tests, we did not observe such relationships for the CPT scores. The AMPT-induced increases in the VAS sleepiness scores and in the more objective OAASS scores were not correlated with the reduced performance on the CPT items. Thus, sedation does not seem to have been a substantial confounding factor in the worsening selective attentiveness observed on AMPT. However, the correlations between OASS overall scores on the one hand, and numbers of hits and of omissions pre-AMPT, and attentiveness scores post-AMPT on the other hand, suggest that there may be some relationship.

We were not able to replicate the previously observed significant correlation between decrease in attentiveness (d') and increase in D_2RBP_{shift} (Verhoeff et al., 2001). This may be due to the fact that the test–retest coefficient of variation for the D_2RBP values derived from [^{11}C]raclopride PET at our center has been reported to be 6% (Jones et al., 1996), thus limiting the sensitivity for interindividual correlational analyses of the AMPT-induced D_2RBP increases, which were on average 13% for our subjects. This may also be the reason why we did not observe any correlation between the AMPT-induced decrease in euphoria and increase in D_2RBP_{shift} that could have been expected given the publications where the pleasurable effects of catecholamine-releasing psychostimulants were correlated with decreases in [^{11}C]raclopride binding (Volkow et al., 1999; Drevets et al., 2001).

As in our previous study the contribution of AMPT-induced increased CPT errors of commission to the attentiveness (d') had been more pronounced, we performed the SST on the last five subjects in the study to inform us more about possible AMPT-induced effects on response inhibition. A trend for an increase in Logan's Stop Signal Response Time (SSRT) was observed but this did not reach significance. Indications for a possible relationship between dopaminergic transmission and response inhibition are mixed. On the one hand, a relationship is suggested by a correlation between response inhibition processing and both positive symptoms in schizophrenic patients at 6 years follow-up and negative symptoms in a psychiatric control group (Wykes et al., 2000), whereas a 48-h AMPT treatment affected both positive and—to a lesser extent—negative symptoms in schizophrenic patients (Abi-Dargham et al., 2000). On the other hand, no correlation between response inhibition processing and both positive and negative symptoms in schizophrenic patients was observed at baseline and no differences were observed in schizophrenic patients on standard versus on newer antipsychotics (Wykes et al., 2000). Thus, in order to obtain more conclusive data, the effects of AMPT on response inhibition will need to be explored in a larger sample.

The lack of any significant changes with AMPT on SCWT scores does not seem to be compatible with a paradigm (Cohen and Servan-Schreiber, 1992) and a PET study (Volkow et al., 1998) that attribute an important role

for DA in the Stroop interference effect. However, our data showed a trend for a decreasing time required to perform the SCWT when only colored letters were presented or when both color and word were matched, but not when color and word were not matched. Thus, it could be that a possible learning effect interfered with our ability to detect a relationship between DA depletion and the Stroop interference effect. Furthermore, the correlations post-AMPT between response times for matched words and both D_2RBP and MHPG levels suggest that catecholaminergic neurotransmission may have an influence on this learning effect. Also, the AMPT-induced decrease in POMS vigor scores as a measure for alertness (McCann et al., 1993) appears to have an influence on this learning effect.

No significant changes were observed with AMPT in OMDR performance. This is in accordance with the unpublished findings in the cohort from our previous study (Verhoeff et al., 2001) and may have been due to the increased variability in performance observed on AMPT. Although scores 5 s after presentation of the dot showed a modest tendency for deterioration on AMPT, the opposite was the case for scores 15 s after presentation. Therefore, it seems that the present study did not have sufficient power to detect any potential deterioration in visuospatial working memory with catecholamine depletion as hypothesized from the literature (Arnsten et al., 1998, 1999).

With AMPT treatment, subjects performed significantly less well during the last 15-s interval of the COWAT. Thus, a worsening performance during the latter part of the 1-min test may be related to catecholamine depletion. Since, in this sample of healthy subjects, very few redundant errors were made (i.e., perseverations of previously mentioned words and production of multiple words with the same roots), we could not detect any changes in "redundance bias" as previously described in schizophrenic patients (Bilder et al., 1992; Szeszko et al., 1999).

Since the FTT results in our study were unaffected by AMPT administration, in accordance with our previous study (Verhoeff et al., 2001), AMPT was found to primarily affect catecholamine transmission in cognitive rather than motor networks. This was similar for D-amphetamine in the study of (Servan-Schreiber et al. (1998b). As in our previous study (Verhoeff et al., 2001), we did not find any significant age effects on FTT scores. Our studies are in contrast with the findings of Volkow et al. (1998), who observed significant and high positive correlations between D_2R availability and FTT scores, both without and with partialing out the significant age effect in their study on both D_2R availability and FTT scores. Given the limited age range in our studies, we do not feel confident that we can rule out an age effect on the FTT scores. The D_2RBP decrease with age is more chronic and is likely to be differentially related to synaptic DA levels and DA transmission than the acute D_2RBP increase on AMPT, therefore resulting in a differential relationship with FTT scores.

5. Conclusion

AMPT decreased plasma catecholamine metabolites and neostriatal D_2RBP in a way and magnitude that was expected from our previous study (Verhoeff et al., 2001) and from other studies (Laruelle et al., 1997; Abi-Dargham et al., 2000; Fujita et al., 2000). Therefore, we are quite certain that adequate dopamine depletion was induced.

The AMPT-induced decreases in measures of positive mood (feeling happy and high) and in measures of alertness (feeling energetic, talkative and vigorous), the increase in measures of sedation (sleepiness, fatigue, objective sedation) and the lack of significant change in measures of negative mood in the healthy subjects in this study are in accordance with the findings from previous studies (McCann et al., 1993; Zimmermann et al., 1996; Salomon et al., 1997; Laruelle et al., 1997; Abi-Dargham et al., 2000; Fujita et al., 2000; Verhoeff et al., 2001). Our study replicated the finding from our previous study (Verhoeff et al., 2001) that the AMPT-induced decrease in happiness is associated with NE rather than DA depletion.

The partial catecholamine depletion resulted in a selective effect on cognitive aspects of attention (CPT) but not on motor aspects of reaction time. As in our previous study (Verhoeff et al., 2001), the effects on attention were not correlated with those on level of sedation. No effects on other measures of motor behavior (ESRS, HNTT, FTT) or on general measures of cognition (WAIS-III tests) were obtained. Therefore, we conclude that the partial catecholamine depletion resulted in a quite selective effect on attention. The previously observed correlation between AMPT-induced attention decrease and neostriatal D_2RBP increase (Verhoeff et al., 2001) could not be replicated, probably due to limited sensitivity of the D_2RBP data for interindividual correlational analyses.

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Investigation Unit, 10th floor, Clarke Division, Centre for Addiction and Mental Health, for support for and management of the subjects during their overnight stay in the psychiatric inpatient unit.

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