PET [^{11}C]DASB Imaging of Serotonin Transporters in Patients with Alcoholism

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Objective: Alcoholism and aggression have each been associated with neurochemical measurements suggestive of decreased serotonin synaptic transmission. We measured densities of the serotonin transporter (SERT) in a moderate-sized sample of alcoholic patients who were assessed for aggressive characteristics.

Methods: Thirty alcoholic inpatients and 18 healthy controls received a PET scan with [^{11}C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile. The alcoholic inpatients were classified as aggressive or nonaggressive based on a comparison between the top third and bottom third scores on the Buss–Durkee Hostility Index.

Results: Using a pixel-wise comparison, no brain region showed significant alterations in SERT binding among the 3 groups of subjects (aggressive alcoholic subjects, nonaggressive alcoholic subjects, and healthy controls) or between the combined alcoholic group and healthy controls. None of the clinical measures (including measures of aggression) correlated with SERT binding in the alcoholic subjects.

Conclusion: Contrary to prior imaging reports using the nonselective ligand [^{123}I]β-CIT, we found no significant alterations of SERT density in alcoholic patients.

Key Words: Positron Emission Tomography, Aggression, Parametric Imaging, [^{11}C]DASB, Serotonin Transporter, Alcoholism.

EPIDEMIOLOGICAL STUDIES HAVE shown that alcohol consumption facilitates aggressive behavior (Parrott and Zeichner, 2002) and is linked to more than 50% of violent crimes and up to 85% of homicides (Murdoch et al., 1990). Prior neurochemical research suggests that both alcoholism and impulsive aggressive behavior are separately or jointly associated with measures interpreted to reflect an overall decrease of serotonin (5-HT) neurotransmission in the brain. For example, several groups have found that serotonin metabolite 5-hydroxyindolacetic acid (5-HIAA) is decreased in the cerebrospinal fluid of subjects with a history of aggression (Roggenbach et al., 2002), patients who attempt suicide (Pitchot et al., 2005), and patients with alcoholism (Heinz et al., 1998). In addition, radioligand imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) has generally found decreased serotonin transporter (SERT) densities in patients with alcoholism (Heinz et al., 1998; Szabo et al., 2004). These imaging studies have limitations, including modest patient samples (e.g., $n = 17$) in Mantere et al. (2002) and Szabo et al. (2004), not distinguishing alcoholic patients with and without a history of aggression (Heinz et al., 1998), and the questionable ability to quantify low neocortical activity after injection of [^{123}I]β-CIT (Kuikka et al., 1995). In addition, all prior studies have used radioligands ([^{123}I]β-CIT or [^{11}C]McN5652) that have significant flaws. The SPECT ligand [^{123}I]β-CIT binds nonselectively to both serotonin and dopamine transporters and has a signal too low in the neocortex to quantify SERT (van Dyck et al., 2000). Although selective for SERT, the PET ligand [^{11}C]McN5652 has low brain uptake and slow brain washout that significantly limits its ability to quantify SERT in the neocortex (Szabo et al., 1995).

Wilson et al. (2002) developed a PET tracer [^{11}C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([^{11}C]DASB) that is selective for SERT, has fast brain uptake and washout appropriate for ^{11}C ($T_{1/2} = 20$ minutes), and has high specific to nonspecific binding that allows quantification in the neocortex. We used this significantly improved PET tracer to measure SERT densities in all

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brain regions of a moderate-sized sample of patients with alcoholism compared with healthy controls.

MATERIALS AND METHODS

Participants

Alcoholic subjects were inpatients who had been abstinent for at least 2 weeks, with an average of 14 ± 2 days abstinence before the PET scan, with these and subsequent data expressed as mean ± SD. Participants were excluded from the study if they had other current Diagnostic and Statistical Manual, 4th ed. (DSM-IV) Axis I diagnoses unrelated to alcoholism, were taking psychotropic medications, had serious organic disease, were claustrophobic, pregnant, had a condition that increases risk for magnetic resonance imaging (MRI), or tested positive for HIV. Healthy subjects were outpatient volunteers and were excluded if they met DSM-IV criteria for alcohol dependence/abuse or any other Axis I disorder, were HIV positive, were pregnant, had a condition that increases risk for MRI, were claustrophobic, or had a serious organic disease.

The study sample consisted of 30 type II (i.e., onset before 25 years of age) alcohol-dependent inpatients (M/F = 24/6, age 39.0 ± 6.1 years) from several ethnic backgrounds including 5 African-American males, 2 African-American females, 4 Caucasian females, 18 Caucasian males, and 1 Hispanic male. Eighteen healthy control subjects (M/F = 9/9, age 36.0 ± 7.1 years) participated in this study including 5 African-American males, 2 African-American females, 4 Caucasian males, 6 Caucasian females, and 1 Asian female. The healthy controls did not have any first-degree relatives who showed alcohol abuse or dependence.

We used the structured clinical interview from the DSM-IV (First et al., 2002). We collected very detailed information on the past and present substance abuse history of the patients using this clinical interview. All of the patients were residing on the inpatient ward of the National Institute of Alcohol Abuse and Alcoholism and were closely monitored. Urine and blood tests were routinely collected on these patients. All subjects were assessed for personality traits with the Neuroticism Extroversion Openness Personality Inventory Revised (NEO-PI-R; Costa and McCrae, 1992), symptoms of depression with the Beck Depression Rating Scale (Beck et al., 1996), hostility and anger with the Buss–Durkee Hostility Index (BDHI; Buss and Warren, 2000), and symptoms of anxiety with the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, 1983). Fifteen alcoholic patients were identified as having nicotine dependence at the time of scan. Healthy controls subjects had no history of current nicotine dependence or abuse.

PET Scan

[^{11}C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile was synthesized as previously described (Wilson et al., 2002). The radiochemical purities of syntheses were 96.0 ± 2.9%, with specific activities of 49.6 ± 10.4 GBq/μ mol at the time of injection.

After an 8-minute transmission scan with a ^{68}Ge rotating rod source, dynamic PET emission scans were acquired on a GE Advance tomograph in the 3-dimensional mode for 120 minutes. Bolus administration of [^{11}C]DASB (703 ± 111 MBq) began at the time the scan started. For all subjects, T1-weighted magnetic resonance images were acquired on a 1.5-T GE Horizon for image coregistration and anatomic reference (TR/TE/x = 24 ms/3 ms/300).

Parametric Image and Data Analysis

Positron emission tomography images were corrected for motion in each subject with Statistical Parametric Mapping2. Parametric images were generated with pixel-wise modeling software (PMOD; version 2.65, PMOD group, Switzerland 2005). Relative blood flow (R_1) and binding potential (BP) parametric images were created using a 2-parameter multilinear reference tissue model MRTM2 with the cerebellar (excluding the vermis) and occipital cortices as the reference regions (Ichise et al., 2003). First, an R_1 was created and coregistered in SPM2 with the subject's MRI. The cerebellum, occipital cortex, raphe, striatum, and thalamus were identified on the coregistered MR image and used to estimate k'_2 (clearance rate constant from cerebellum and occipital to plasma) by MRTM. The placement was performed by the same researcher for all subjects. MRTM2 used k'_2 to create parametric images of binding potential. We spatially normalized all BP images to a custom template created in SPM2 of all R_1 images. Subject groups were compared on a pixel-wise basis with SPM2 and volumes of interest. The latter were identified with an automated anatomical template from the Montreal Neurological Institute (MNI) by identifying the regions of interest (Tzourio-Mazoyer et al., 2002). Eight regions that have moderate to high SERT density were selected from the template and applied, one by one, as a mask to each subject's BP image spatially normalized to the MNI space. The mean BP of the 8 regions were then compared between the 3 groups. The raphe was manually defined and had a volume of 1.352 cm^3. The mean BP of the 9 regions was then compared between the groups. All images were analyzed by the same researcher.

RESULTS

Demographics and Behavioral Measurements

All patients were alcohol dependent and had long histories of alcohol dependence, with an average of 23 years for the alcoholic group (Table 1). All alcoholic patients and control groups were matched for age, sex, and PET parameters, with the exception that the control group had

Table 1. Participant Demographics and Clinical Measures

Measure	**Alcoholic** subjects (N = 30)	**Controls** (N = 18)	p
Age	39.3 ± 8.6	36.4 ± 9.39	0.275
Education[a]	12.8 ± 2.3	15.2 ± 2.7	0.002*
Injected activity (MBq)	19.7 ± 1.0	19.8 ± 58	0.756
Specific activity (MBq/μmol)	1885 ± 604	2064 ± 378	0.276
Injected mass (nmol)	10.2 ± 2.3	10.0 ± 2.5	0.786
Years alcohol exposure[b]	23.2 ± 5.3	0	0.0001*
Beck depression scale[b]	9.1 ± 9.8	2.5 ± 3.9	0.002*
BDI (hostility)[b]	57 ± 10.7	44 ± 9.4	0.001*
BDI (anger)[b]	55 ± 12.3	40 ± 5.9	0.001*
BDI (verbal aggression)[b]	57 ± 9.4	48 ± 9.1	0.01*
BDI (physical aggression)[b]	59 ± 10.7	44 ± 6.9	0.001*
BDI (total score)[b]	58 ± 10.1	42 ± 7.8	0.001*
Neuroticism[b]	60 ± 11.7	47 ± 10	0.0001*
Extroversion	53 ± 9.8	52 ± 12	0.471
Openness	51 ± 9.5	51 ± 12	0.971
Agreeableness[a]	41 ± 8.7	52 ± 8.5	0.0001*
Conscientiousness	44 ± 14	50 ± 9.5	0.117
STAI (trait anxiety)[b]	43 ± 13	30 ± 6.6	0.0001*
STAI (state anxiety)[b]	33 ± 11	26 ± 6.6	0.008*

Values for neuroticism, extroversion, openness, agreeableness, and conscientiousness are the T-scores from the NEO-PI-R instrument.

Data represent mean ± SD. p Values by independent T-tests.

*$p < 0.05$.

[a]Controls > alcoholics.

[b]Alcoholics > controls.

more years of education than the alcoholic group ($p \leq 0.002$).

[^{11}C]DASB SERT Imaging

Binding potential is proportional to SERT density. Statistical Parametric Mapping2 assessed *BP* images from the 3 groups with a statistical threshold of 0.05 by family-wise error. No brain regions showed statistically significant differences among the 3 groups (aggressive, nonaggressive, and controls) or when the combined alcoholic and healthy subject groups were compared. All of the regions examined (parahippocampus, occipital cortex, thalamus, frontal cortex, amygdala, hippocampus, raphe, anterior cingulate, caudate, and putamen) by placing volumes of interest showed statistically insignificant differences among the 3 groups or between the combined alcoholic and control groups (Table 2). A recent postmortem study found decreased SERT in the caudate of patients with alcoholism (Storvik et al., 2006). For this reason, we included striatal structures in this volume of interest analysis but found nonsignificant changes.

As the cerebellum is susceptible to atrophy in patients with alcohol dependence, we analyzed the imaging data with an additional reference region. We chose the occipital cortex because it showed low SERT *BP* values (Table 2) that approximate nondisplaceable uptake and because it is an uncommon site for atrophy in alcoholism. As the occipital cortex has slightly higher uptake than the cerebellum, the "binding potential" values "*BP*" with the occipital cortex as the reference region were 20 to 50% lower than the *BP* using the cerebellum (Table 3). Nevertheless, the revised SERT "*BP*" values again showed no significant differences among the 3 groups or between the total alcohol and control groups. This analysis strongly suggests that the original results using the cerebellum as a reference region were not artifactually influenced by possible cerebellar atrophy in the alcoholic patients.

Alcoholic subjects who had current nicotine dependence were also examined and did not differ from nonsmokers in SERT density.

Table 2. Serotonin Transporter Binding Potential from Automated Volume of Interest Analysis

Region	Alcoholics	Controls
Thalamus	0.900 ± 0.053	1.431 ± 0.187
Frontal cortex	0.158 ± 0.062	0.170 ± 0.061
Amygdala	1.280 ± 0.118	1.247 ± 0.198
Hippocampus	0.710 ± 0.098	0.695 ± 0.104
Parahippocampus	0.630 ± 0.192	0.626 ± 0.128
Raphe	2.544 ± 0.462	2.409 ± 0.364
Anterior cingulate	0.300 ± 0.035	0.325 ± 0.083
Caudate	0.520 ± 0.047	0.527 ± 0.004
Putamen	1.000 ± 0.100	1.001 ± 0.033

Values represent regional binding potentials (mean ± SD). All brain regions showed statistically insignificant differences among the aggressive, nonaggressive, and healthy control groups.

Table 3. Serotonin Transporter "Binding Potential" from Automated Volume of Interest Analysis Using the Occipital Cortex as the Reference Region

Region	Alcoholic subjects	Controls
Thalamus	0.744 ± 0.021	0.651 ± 0.052
Frontal cortex	0.072 ± 0.042	0.071 ± 0.044
Amygdala	0.825 ± 0.039	0.781 ± 0.067
Hippocampus	0.400 ± 0.012	0.365 ± 0.001
Parahippocampus	0.317 ± 0.026	0.343 ± 0.025
Raphe	1.760 ± 0.569	1.493 ± 0.285
Anterior cingulate	0.156 ± 0.021	0.148 ± 0.041
Caudate	0.424 ± 0.016	0.362 ± 0.027
Putamen	0.783 ± 0.046	0.674 ± 0.040
Cerebellum	0.078 ± 0.128	0.073 ± 0.124

Values represent regional binding potentials (mean ± SD). All brain regions showed statistically insignificant differences among the alcoholic subjects and healthy control groups using the cerebellum as the reference region.

"Binding potential" is placed in quotation marks for this Table and text to distinguish these values from the more typical binding potential using the cerebellum as the reference region.

We used SPM2 to determine potential correlations of *BP* images using age as a nuisance variable with all 13 behavioral tests, including measures of aggression (Table 1). Serotonin transporter binding was not correlated with any of the clinical measurements in any of the 3 groups or the combined group of alcoholic patients. To assess further the possible correlations with aggression, we compared SERT *BP* with aggression after 2 different subgroupings of the entire sample of alcoholic subjects: (1) a median split based on the Buss–Durkee aggression total score, thereby creating 2 groups of 15 each and (2) 2 groups of 10 each with the highest and lowest scores on the Buss–Durkee total score. No brain region had significant alterations of SERT density when comparing these 2 subgroups (i.e., top vs bottom half and top vs bottom third).

DISCUSSION

Five prior publications have reported SERT densities in subjects with alcoholism or aggression. The studies in alcoholics have found: (1) widespread decrease of SERT measured with [^{11}C]McN5652 (Szabo et al., 2004) and (2) decreased brainstem SERT with [^{123}I]β-CIT in male alcoholic subjects (Heinz et al., 1998). The studies of aggression found (1) decreased SERT with [^{11}C]McN5652 in anterior cingulate of subjects with impulsive aggression (Frankle et al., 2005), and (2) decreased brainstem SERT with [^{123}I]β-CIT in violent offenders compared with either nonviolent alcoholic subjects or controls (Tiihonen et al., 1997). The consensus of these reports is that both alcoholism and aggression are associated with decreased SERT, which the authors have generally interpreted to reflect decreased serotonin neurotransmission.

As noted in the introduction, this study was designed to test this consensus using a moderate sample size and arguably the best available PET ligand for SERT—namely,

[^{11}C]DASB. We found no significant differences in SERT densities in alcoholic subjects using either a pixel-wise comparison with SPM2 or a volume of interest analysis. In addition, we found no correlation between measures of aggression and regional SERT densities. The clinical characteristics of the patients in our study were similar to that of Heinz et al. (1998, 2002), and the patients came from the same NIAAA inpatient unit.

The reasons for the discrepant results are not clear, but include the possible influence of sex, smoking, genotype, and endogenous serotonin on radioligand binding, technical performance of the various tracers, and time of PET scan relative to alcohol withdrawal. We will discuss each of these potential causes of the discrepancies between our and prior studies.

Sex

Heinz et al. (1998, 2002) found decreased brainstem SERT in male ($n = 22$) but not female ($n = 9$) alcoholic subjects. We examined the effect of sex in our sample and found no regions with significant differences in male versus female alcoholic subjects, male alcoholic subjects versus male controls, or female alcoholic subjects versus female controls.

Smoking

Using the nonselective SPECT radioligand [^{123}I]β-CIT, Staley et al. (2001) demonstrated modesty higher SERT binding in the brainstem of smokers versus nonsmokers, and increased SERT in females irrespective of smoking status compared with male subjects (Staley et al., 2001). Our study examined smoking by gender interactions and SERT binding potential and found no differences between the alcoholic and control groups.

Genotype

A functional variant has been described in the promoter region of the SERT gene, *SLC6A4* (Lesch et al., 1996). The 2 abundant alleles at this polymorphism are designated long (*l*) or short (*s*) on the basis of the number of copies of an imperfect repeat sequence. Homozygosity for the long allele (*ll*) is associated in vitro with increased SERT density and function (Lesch et al., 1996). In a small sample size, an SPECT study using [^{123}I]β-CIT found a significant relationship of this SERT polymorphism and receptor binding in the dorsal brainstem of male volunteers (Heinz et al., 2000). In contrast, another study with a larger sample size found no association using the same SPECT radioligand (van Dyck et al., 2004). We do not have genotyping data for our subjects. This polymorphism is, however, unlikely to have removed differences between alcoholic subjects and healthy subjects, unless the effect of genotype is much larger than previously reported and unless the polymorphisms were disproportionately distributed in the 2 groups.

Endogenous Serotonin

The effect of endogenous serotonin on binding of [^{11}C]DASB was examined in healthy subjects following dietary tryptophan depletion. The resulting decrease of brain serotonin had no effect on [^{11}C]DASB binding (Talbot et al., 2005), suggesting that endogenous concentrations of this neurotransmitter did not significantly confound our study.

Length of Withdrawal

Our patients were studied approximately 2 weeks after abstinence confirmed on an inpatient unit. This interval was less than the 3 to 5 weeks used by Heinz et al. (1998) and the several years of abstinence used by Szabo et al. (2004).

Summary

We can think of 2 possible reasons for the discrepancy of our results and prior publications—namely, the imaging procedure or the period of withdrawal. Prior studies used a ligand that either is not selective for SERT ([^{123}I]β-CIT) or has high nonspecific binding ([^{11}C]McN5652). For procedure, we suspect that the current results are more accurate, as [^{11}C]DASB is a superior radioligand. As to the period of withdrawal, additional studies are necessary to determine whether this parameter significantly affects SERT densities.

CONCLUSION

We found no significant differences in SERT binding in alcoholic patients compared with healthy subjects and no correlation with psychological measures of aggression. This finding was confirmed using both the cerebellum, which is vulnerable to atrophy in alcoholism and the occipital cortex as reference regions. Although contradictory to prior reports, the current study used a moderate-sized subject sample and a PET radiotracer selective for SERT relative to other monoamine transporters.

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