Striatal Enlargement in Rats Chronically Treated with Neuroleptic

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Background: *Striatal enlargement with chronic neuroleptic treatment in schizophrenic patients has been reported by several investigators. Longitudinal magnetic resonance imaging studies of patients suggest that changes in striatal volume may be caused by treatment with antipsychotic medication.*

Methods: *We have examined the effects of chronic neuroleptic treatment on postmortem striatal volume in the laboratory rat and have examined the relationship between striatal volume and vacuous chewing movements (VCMs). Autoradiographs of 50 rats treated with haloperidol (1.5 mg/kg/day) or drug free for varying durations of time (1–12 months) were utilized in this analysis.*

Results: *Chronic treatment with neuroleptics (1 month or greater) was associated with larger striatal volumes. The increase in striatal volume was present at 1 month of treatment and was sustained to 12 months of treatment. Rats that developed the high-VCM syndrome had larger striatal volumes than both drug-free and low-VCM rats, while low-VCM rats had larger striatal volumes than drug-free rats.*

Conclusions: *These data suggest that chronic neuroleptic treatment is the cause of striatal enlargement in the laboratory rat, and that this enlargement is most prominent in rats that have the high-VCM syndrome.* Biol Psychiatry 1998;44:675–684 © *1998 Society of Biological Psychiatry*

Key Words: Tardive dyskinesia, chronic antipsychotic, rats, striatum, vacuous chewing movements

Introduction

Postmortem and magnetic resonance imaging (MRI) studies have described basal ganglia enlargement in schizophrenic patients chronically treated with neuroleptics (Andreasen et al 1986; Delisi et al 1991; Frazier et al 1996a, 1996b; Heckers et al 1991; Hokama et al 1995; Jernigan et al 1991; Nasrallah et al 1993; Swayze et al 1992). This is in contrast to the usual pattern of neuropathology in schizophrenia, where reductions in the size of gray matter brain structures and enlargement of fluid-containing structures are characteristically seen (Bogerts 1991; Hyde et al 1991). Since these studies were cross-sectional and predominantly included patients chronically treated with neuroleptics, it was not clear whether striatal enlargement reflected a disease-related abnormality (Jernigan et al 1991; Swayze et al 1992), or might be an effect of chronic treatment (Chakos et al 1994; Keshavan et al 1994). The finding of striatal enlargement in schizophrenic persons has been interpreted by some investigators as a feature of the pathology associated with the disease caused by a disturbance in neuronal pruning of subcortical structures during development (Jernigan et al 1991; Swayze et al 1992). Alternatively, other investigators have proposed the striatal enlargement may be the result of chronic treatment of the illness with antipsychotics. This hypothesis is suggested by two longitudinal MRI studies of first-episode schizophrenic patients that report within-subject increases in caudate nuclei volumes after chronic neuroleptic treatment (Chakos et al 1994; Keshavan et al 1994).

Previous studies using chronic antipsychotic drug treatment in laboratory rats have demonstrated a number of behavioral (Clow et al 1980; Gunne et al 1982, 1984, 1986; Ellison et al 1987; Kakigi et al 1995; Tamminga et al 1990; Waddington et al 1986), neurochemical (Egan et al 1994; Gunne et al 1984; Kaneda et al 1992; Mithani et al 1987; Tamminga et al 1990; Waddington 1990), and structural (Benes et al 1983, 1985; Bernard et al 1991; Delfs et al 1995; Egan et al 1994; Meshul and Casey 1987; Muller and Seeman 1997; Roberts et al 1995) changes associated with this treatment. Where comparisons have been made, the behavioral and neurochemical changes in rat striatum often are similar to human striatal changes with neuroleptic treatment (Waddington et al 1986; Waddington 1990); however, there has been no morphometric study of rats (or other nonhuman species) to corroborate

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the volumetric findings reported in human in vivo imaging studies. In this study, we examined the effect of chronic neuroleptic treatment on striatal volume in the laboratory rat. We also examined the relationships between striatal volume and several other neuroleptic-induced changes, including striatal glucose metabolism and drug-induced vacuous chewing movements (VCMs).

Methods and Materials

Animals

Male Sprague-Dawley (SD) albino rats were obtained from Charles River (Wilmington, VA). Rats that initially weighed 200–250 g were housed in groups of 3 or 4 and kept on a 12-hour light–dark cycle, at a constant room temperature of 21°C. Rats were treated with either vehicle (plain drinking water) or haloperidol 1.5 mg/kg/day, the same dosing technique (oral with drinking water), and the same blind behavioral assessment detailed below. We report data from $n = 30$ haloperidol-treated rats and $n = 20$ water-control rats.

Drug Administration

Rats were treated with either haloperidol, 1.5 mg/kg/day, prepared as a solution and given in drinking water, or vehicle (plain drinking water). For dosing, haloperidol was dissolved in a minimum volume of glacial acetic acid. This solution was diluted with distilled water, and the pH was adjusted to 5.5–6.0, using 10 N sodium hydroxide, to give a stock solution of 0.25 mg/mL. The stock was diluted for daily dosing to give a drug concentration of 0.025 mg/mL in drinking water. Rats were divided into six treatment groups: 14 rats treated for 1 month before sacrifice (group 1, drug free, $n = 7$; group 2, haloperidol, $n = 7$); 18 rats treated for 6 months (group 3, drug free, $n = 6$; group 4, haloperidol, $n = 12$); and 18 rats treated for 12 months (group 5, drug free, $n = 7$; group 6, haloperidol, $n = 11$). Previous analyses of plasma from rats show that this dosing technique produces plasma haloperidol levels of 5.2 (3.0) ng/mL with chronic treatment (Kaneda et al 1992; Tamminga et al 1990), a plasma level that in humans is within the haloperidol therapeutic range. Moreover, the dose of haloperidol at 1.5 mg/kg/day in the rat produces D2 receptor up-regulation in the striatum (137%) and gamma-aminobutyric acid A (GABAA) receptor up-regulation in the substantia nigra pars reticulata (116%; Shirakawa and Tamminga 1994).

Volumetric Assessment of Tissue

Autoradiographs of coronal brain slices, prepared from 14C-2-deoxyglucose (2DG)-injected rats for cerebral metabolism determinations (Sokoloff et al 1977), were available from 50 rats for volumetric determination. Autoradiographs of slices that correspond to Plate 10 through Plate 19 of the Paxinos Rat Brain Atlas (Paxinos and Watson 1986) were utilized. Autoradiographic slices at every 200 μm between those coronal plates (comprising approximately 13 slices) were digitized using a Compaq computer-based image analyzer (Loats, Westminster, MD), and striatal area measurements from those slices were obtained utilizing the program NIH image (Rasband, Bethesda, MD). Plate 10 was identified on the 2DG films by the characteristic increasing prominence of the striatum and decreasing prominence of the nucleus accumbens. Plate 19 was identified by the appearance of the globus pallidus and the increasing bulbosity of the anterior commissure. The superior boundary of the striatum was defined by the forceps minor corpus callosum, the lateral boundary by the external capsule, and the medial boundary by the lateral ventricle and the corpus callosum. These boundaries were manually outlined. The inferior boundary of the striatum is a boundary between gray matter structures and was determined by identification of predetermined landmarks. Two lines were drawn to delineate this boundary: one line drawn from the rhinal fissure to the anterior commissure; and another line from the notch of lateral olfactory tract, through the anterior commissure, and extending toward the lower boundary of the lateral ventricle or corpus callosum. After all boundaries of the striatum were determined by this method, an automatic mensuration function was utilized to better delineate boundaries between gray and white matter within the region where the operator-determined boundaries had been defined. Area measurements of the striatal slice were obtained, and the volume of the anterior striatum was then calculated utilizing the formula for postmortem volumes established by Van Eden and Uylings (Van Eden and Uylings 1985):

$$\text{volume} = \sum_{i=1}^{n-1} [\tfrac{1}{2}[(Ai + (Ai + 1)] \text{ multiplied by } di$$

where Ai = area of the ith section; n = the number of sections measured; and di = distance between surface areas Ai and $Ai + 1$, calculated from the mean thickness of the sections multiplied by the number of the sections skipped between successively measured sections.

The anterior brain volume was derived using an automatic mensuration function of NIH image to measure the area of the brain in the same digitized images that were utilized to determine the volume of the anterior striatum.

All measurements were performed by a single operator (MHC) under blind conditions. Use of autoradiographs of coronal brain slices, prepared from 2DG-injected rats, resulted in excellent delineation of boundaries between the gray matter of the striatum and white matter tracts that surround it. This method allowed us to obtain intrarater and interrater reliability of .97 and .98 in measurement of the anterior striatal volume and the anterior brain volume, respectively.

Determination of Regional Cerebral Metabolic Rates of Glucose Metabolism

The procedure was carried out as previously described (Tamminga et al 1987). Regional cerebral metabolic rate of glucose metabolism (gCMR) was measured using the 2DG method of Sokoloff (Sokoloff et al 1977). Rats were killed 45 min after 2DG injection by an overdose of sodium pentobarbital (50 mg/rat), administered intravenously. The brains were removed, frozen in chilled isopentane (−45°C), and stored at −80°C. Coronal sections (20 μm) were cut from all brains in a cryostat and mounted on cover glasses. Autoradiographs were developed

Table 1. Raw and Adjusted Volumes and Striatal-Brain Ratios

	Drug free (n = 30)		Adjusted volume[b]	Drug treated (n = 20)		Adjusted volume[b]
	Raw volume			Raw volume		
	Mean	(SD)	Mean	Mean	(SD)	Mean
Anterior Striatal Volume (mm^3)[a]						
One Month	58.589	(5.345)	57.633	58.827	(6.932)	59.771
Six Months	59.609	(12.595)	58.919	62.599	(10.700)	61.318
Twelve Months	57.215	(3.352)	59.916	62.079	(7.312)	61.360
Anterior Brain Volume (mm^3)						
One Month	258.250	(20.852)		250.711	(25.865)	
Six Months	257.194	(50.733)		259.520	(37.523)	
Twelve Months	243.735	(18.621)		257.311	(25.165)	
Striatal-Brain Ratio[c]						
One Month	22.683	(0.790)		23.468	(1.429)	
Six Months	23.132	(0.647)		24.046	(1.265)	
Twelve Months	23.514	(0.881)		24.113	(1.655)	

[a]When we utilized ANCOVA to examine anterior striatal volume with drug treatment and duration of treatment as grouping factors and anterior brain volume as a covariate, there was a main effect of drug treatment (F = 5.53; df = 6,43; p = .023) and no effect of duration of treatment (F = 1.80; df = 6,43; p = .178).

[b]Anterior striatal volumes are adjusted for brain size.

[c]When we utilized ANOVA to examine striatal-brain ratio with drug treatment and duration of treatment as grouping factors, there was a main effect of drug treatment (F = 5.31, df = 5,44; p = .026) and no effect of duration of treatment (F = 1.67; df = 5,44; p = .200).

by exposing brain sections on Kodak MIN-R X-ray film for 14 days. Regional glucose metabolisms were calculated from brain and plasma radioactivity and plasma glucose concentrations.

Assessment of Oral Movements

Rats were rated by trained and experienced raters who were blind to treatment condition. Individual rats were observed in an entirely empty, small (20 × 30 × 23) Plexiglas cage. Animals were allowed 2 min to accommodate to the rating cage before movements were quantified. Jaw movements were counted for 5 min, stopping the count whenever grooming or jaw tremors began (Kaneda et al 1992). Ratings were carried out at least as frequently as once at baseline, and every month thereafter, with two ratings being performed in the last 2 weeks prior to sacrifice. An average of the final two ratings was taken as the final VCM score.

Rats treated with haloperidol 1.5 mg/kg/day were dichotomized into two groups based on the VCM rates. Rats with eight or more VCMs/5 min were classified into a high-VCM or dyskinetic group, and those with less than eight VCMs/5 min were classified into a low-VCM or nondyskinetic group (Hashimoto et al in submission).

Analysis

Repeated-measures analysis of variance (ANOVA), with drug treatment and duration of treatment as between-subject factors, hemisphere as a within-subject factor, and striatal volume as the dependent variable was performed. Correlates of striatal volume were determined using Pearson's correlation coefficient. Then regression analysis (utilizing dummy variables for categorical variables) was utilized to assess the predictive value of striatal gCMR and neuroleptic status on striatal volume. Repeated-measures ANOVA was also used to examine the relationship between VCM groups (drug free, low VCM, and high VCM), hemisphere, and striatal volume. In this analysis the drug-free group was compared to two neuroleptic-treated groups (low VCM and high VCM).

As reflected in the raw data in Table 1, there was considerable variability in anterior striatal volumes. Therefore, striatal volumes were adjusted in two ways to control for brain size variability:

1. *The ANCOVA adjustment method.* Anterior brain volumes were utilized as a covariate in an analysis of covariance (ANCOVA), with anterior striatal volume as the dependent variable.
2. *The ratio adjustment method.* To stabilize variances, data were transformed using a ratio method. The ratio of the right or left anterior striatal volume/anterior brain volume was multiplied by 100 to obtain a measure of striatal size volume.

Both of these methods of transforming data sets are routinely utilized in assessing brain structure volumes in morphometry. These methods are equally effective in detecting significant differences between groups and are more sensitive in detecting differences than are raw data sets (McIntosh et al 1996). In the present study, all analyses involving striatal volume were performed by both methods, and the results obtained by either method were the same (Table 1). Therefore, we will report the results on 50 rats utilizing the striatal–brain ratio adjustment method.

Results

Neuroleptic Treatment and Duration of Treatment

To examine the effect of neuroleptic treatment and duration of treatment on striatal volume, we performed an

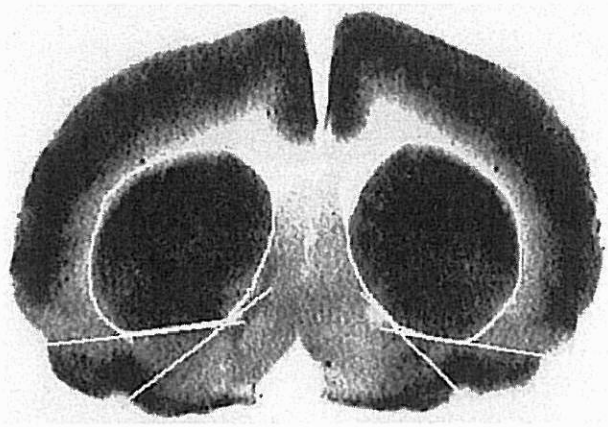

Figure 1. Boundary delineation for area measurement of anterior striatum.

ANOVA with striatal–brain ratio as the dependent variable, drug status and duration of treatment as between-group factors, and hemisphere as a within-group repeated factor. There was a main effect of drug treatment (F = 5.31; df = 5,44; p = .026; Figure 1), with drug-treated animals having a larger striatal–brain ratio than drug-free animals. There was no main effect of duration of treatment (F = 1.67, df = 5,44; p = .200) and no main effect of hemisphere (F = 2.27; df = 5,44; p = .139). There was no interaction between drug status and treatment duration (F = .08; df = 5,44; p = .923), suggesting that the volume increase in drug-treated animals was present in the 1-month treatment group and persisted in the 12-month treatment group. Since there was a main effect of drug treatment and no interactions between drug treatment and treatment duration, the effect of drug treatment on striatal volume was significant at each treatment duration.

To evaluate the effects of drug treatment on total anterior brain volume, we performed an ANOVA with anterior brain volume as the dependent variable and drug treatment and duration of treatment as between-subject factors. There was no main effect of drug treatment on anterior brain volume (F = 0.09; df = 5,44; p = .762) or treatment duration (F = 0.26; df = 5,44; p = .774), and there were no interactions (F = .44; df = 5,44; p = .647).

Correlates of Striatal Volume

Larger striatal–cortical ratios were associated with greater average VCM number (r = .281, $p < .05$) and neuroleptic treatment (r = .344, p = .015) (Table 2). There was no association between striatal volume and lateral striatal gCMR (r = .089, p = ns) or medial striatal gCMR (r = −.93, p = ns). We performed a multiple regression analysis with striatal–brain ratio as the dependent variable, categorical predictors entered as dummy variables, and predictor variables entered simultaneously. Striatal glucose utilization did not predict striatal volume, whereas neuroleptic status did predict striatal volume (Table 3). This suggests that changes in striatal volume did not simply reflect changes in the spread of metabolic activity. The results were the same when the analysis was performed stepwise.

VCM Group and Duration of Treatment

Animals were divided into three groups (drug free; neuroleptic treated, low VCM; neuroleptic treated, high VCM) based on neuroleptic exposure and rate of VCMs (Hashimoto et al in submission; Table 4). The high-VCM group had 30.35 (22.39) VCM/5 min. This was more than either the low-VCM or drug-free group, which both had approximately 5 VCM/5 min ($p < .05$). Time on neuroleptic was not significantly different in the high- and low-VCM groups (t = −1.57; df = 13.72; p = .140; Table 4).

To determine whether there was an effect of VCM status on striatal–brain ratio, we performed an ANOVA with the striatal–brain ratio as the dependent variable, VCM group as the between-subject factor, and hemisphere as the within-subject factor. There was a main effect of VCM group (F = 3.54; df = 5,44; p = .037; Figure 2). Post hoc comparisons for one between-subject and one within-subject factor using a modified Tukey pairwise

Table 2. Pearson's Correlation Coefficient *(r)*

	Lateral striatal gCMR (N = 45)	Medial striatal gCMR (N = 45)	Stratial-brain ratio (N = 50)	Drug Status (N = 50)	# VCM/5min (N = 50)
Treatment Duration	−0.394**	−0.537**	0.263	0.082	0.297*
Neuroleptic Status	−0.234	−0.268	0.344*	1.000	0.444**
# of VCM/5 minutes	−0.198	−0.225	0.281*	0.443**	1.000
Lateral Striatal gCMR	1.000	0.961**	−0.089	−0.234	−0.199
Medial Striatal gCMR	0.961**	1.000	−0.092	0.268	−0.225
Striatal-Cortical Ratio	−0.089	−0.093	1.000	0.344*	0.281*
Weight	−0.487**	−0.607**	0.109	0.047	0.289

*$p < .05$; **$p < .01$.

Table 3. Predictors of Striatal-Brain Ratio

Predictors Entered Simultaneously Source	Beta	T	Significance
Neuroleptic Status	0.344	2.239	0.032*
Weight	0.253	1.221	0.229
Glucose Utilization-Medial Striatum	0.547	0.829	0.412
Glucose Utilization-Lateral Striatum	−0.411	−0.692	0.493
Predictors Entered Stepwise			
Source	Beta	T	Significance
Neuroleptic Status	0.319	2.213	0.032*

*$p < .05$.

comparison revealed that the high-VCM group had a larger average striatal volume than did both the drug-free group and the low-VCM group ($p < .05$; Figure 3; Table 4). In addition, the low-VCM group had a larger striatal volume than the drug-free group. There was no main effect of hemisphere, and there were no interactions.

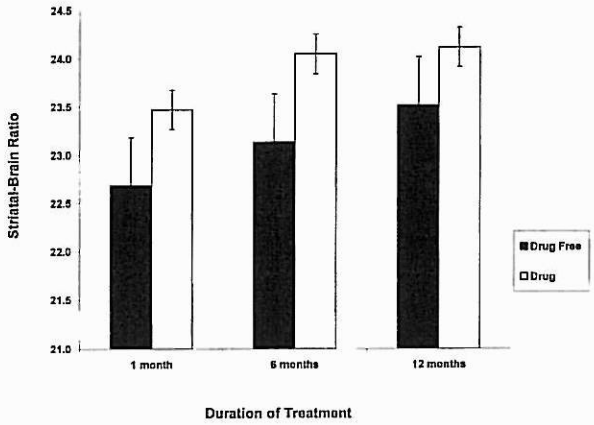

Figure 2. Striatal-Brain Ratio by Drug Status and Duration of Treatment. There is a main effect of drug treatment, with drug treated rats having larger striatal volumes than drug free rats ($F = 5.31$, df = 44,5; $p = .026$). The effect of duration of treatment is not significant ($F = 1.67$; df = 5,44; $p = .20$). The drug by time interaction is not significant ($F = .08$; df = 5,44; $p = .923$).

Discussion

This study of the effects of neuroleptic treatment on striatal volume in rats was initiated due to previous findings of striatal enlargement in chronically treated schizophrenic patients and an increase in caudate nuclei volumes of first-episode schizophrenic patients after 12–18 months of neuroleptic treatment (Chakos et al 1994; Keshavan et al 1994). Since human comparison subjects cannot be treated chronically with neuroleptics, it had not been possible to determine conclusively that the striatal enlargement in patients was an effect of neuroleptic treatment, rather than due to the pathophysiology of schizophrenia.

Effects of Chronic Neuroleptic Treatment in the Rat

In the current study there was striatal enlargement in rats after chronic neuroleptic treatment (at least 1 month). The increase in striatal volume in neuroleptic-treated animals was apparent at 1 month, and subsequent neuroleptic exposure was not associated with further changes. The increase in striatal size was also not associated with hemisphere or striatal glucose utilization rate, but was associated with the high-VCM syndrome.

We reviewed previous studies of the anatomic and biochemical effects of chronic neuroleptic treatment to suggest a possible basis for the neuroleptic-induced striatal volume increases reported in this study. Many of the biochemical and anatomic effects of chronic neuroleptic treatment occur within 1 month of treatment (Bernard et al 1991; Bowers 1984; Buchsbaum et al 1987; Chiodo and Bunney 1987; Delfs et al 1995; Eastwood et al 1994; Hyman and Nestler 1993; Meshul and Casey 1987; Muller and Seeman 1977). These effects include an increase in firing rates of midbrain dopamine neurons, followed by depolarization inactivation (Chiodo and Bunney 1987); an increase in dopamine turnover reflected by an increase in plasma homovanillic acid (Bowers 1984); an increase in striatal D2 receptor messenger (m)RNA (Bernard et al 1991; Muller and Seeman 1977); an increase in glucose striatal utilization (Buchsbaum et al 1987); an increase in glutamic acid decarboxylase (GAD) mRNA in the striatum (Delfs et al 1995); an increase in synaptophysin

Table 4. Oral Dyskinesias and Striatal-Brain Ratio in Haloperidol-Treated and Drug Free Rats

	Drug free ($N = 20$)		Low VCM group ($N = 9$)		High VCM group ($N = 21$)	
	Mean	SD	Mean	SD	Mean	SD
VCMs/5 minutes	5.07	(6.66)	4.53	(2.24)	30.35**	(22.39)
Striatal-Brain Ratio	23.11	(0.82)	23.67	(1.34)	24.05*	(1.29)
Time on Neuroleptic	none		5.11	(4.54)	7.857	(4.04)

*Striatal-brain ratio in high VCM group is significantly larger than vehicle treated group ($p < .05$).
**High VCM group has more VCMs/5 minutes than either low VCM or Drug Free Group ($p < .001$).

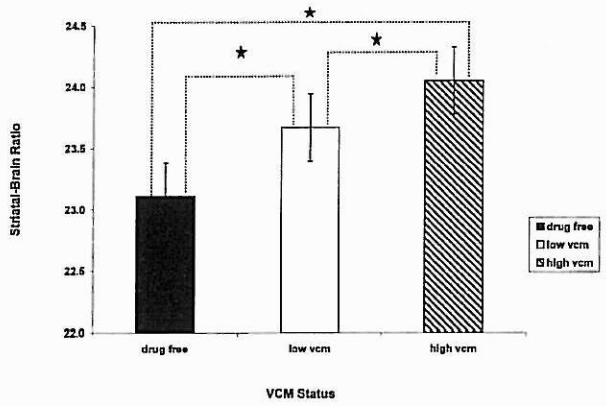

Figure 3. Striatal-Brain Ratio by VCM Status. There was a main effect of VCM Status ($F = 3.54$; df = 2,47, $p = .037$). Star (★) between two group indicates a significant group difference by Tukey posthoc comparison for one between subject and one within subject factor ($p < .05$).

mRNA in the dorsolateral striatum (Eastwood et al 1994); activation of the immediate early gene c-fos and zif268 mRNA in the basal ganglia (Hyman and Nestler 1993); and an increase in perforated postsynaptic densities in the caudate (Meshul and Casey 1987). Additional anatomic and biochemical effects that occur with chronic antipsychotic treatment have been reported, even though a detailed analysis of their time course is often not available. These changes include: a neuroleptic-induced increase in neuronal size of 13% in the striatum, an increase in the size of axon terminals in 15% of the neuronal population in the striatum, and collateral sprouting of axons in the substantia nigra after 16 weeks of treatment (Benes et al 1983, 1985); a neuroleptic-induced decrease in excitatory axospinous corticostriatal asymmetric synapses in the striatum after 6 months of treatment (Roberts et al 1995); GABAA receptor up-regulation in the substantia nigra with 6 months of treatment (Shirakawa and Tamminga 1994); and increased mRNA for dynorphin and enkephalin in the striatum after 9 months of treatment (Egan et al 1994).

Of the biochemical and structural changes that occur between 1 and 6 months of standard antipsychotic treatment, we can speculate with regard to the changes that may be associated with striatal enlargement. It is possible that striatal enlargement with neuroleptic treatment reflects an increase in the cellular interstitial fluid due to the increase in metabolic activation in the basal ganglia with neuroleptic treatment (Buchsbaum et al 1987); however, in the current study, glucose cerebral metabolism was not a significant predictor of striatal volume. It is also possible that the increase in the striatal volume may reflect D2 receptor density. It is conceivable that long-term neuroleptic treatment could result in a bimodal distribution of D2 receptors (Seeman 1984); however, in this study the bimodal distribution of striatal volume in neuroleptic-treated rats was also associated with severity of the VCM syndrome. It is also unlikely that the increase in the striatal volume reflects changes in D2 receptor density, since prior studies have demonstrated that D2 receptor mRNA levels do not differ in high-VCM and low-VCM rats (Egan et al 1994). Finally, it is probable that the 13% increase in the size of striatal neurons and axon terminals after chronic neuroleptic treatment (Benes et al 1985) is related to the striatal volume increase, but the specific mechanism for this increase in neuronal size is not clear.

In the current study, striatal volume in the high-VCM group is larger than in either the drug-free group or the low-VCM group. The difference between the high-VCM group and the low-VCM group is not due to a difference in treatment duration, since treatment for more than 1 month is not associated with further increases in striatal volume. Therefore, the greater degree of striatal enlargement in the high-VCM group may be related to the pathophysiology of the VCM syndrome and/or to pretreatment neurobiologic factors that render some animals more susceptible to it.

To consider possible mechanisms underlying the relationship between the high-VCM syndrome and striatal enlargement, we reviewed the biochemical and anatomic changes in the brains of rats with the high-VCM syndrome that have been previously reported (Shirakawa and Tamminga 1994; Gunne et al 1984; Roberts et al 1995). Changes that are specifically associated with high-VCM syndrome include a decrease in D1 receptor density in the substantia nigra (Shirakawa and Tamminga 1994), a decrease in GAD in the globus pallidus and substantia nigra (Gunne et al 1984), and mitochondrial hypertrophy with a decrease in inhibitory axodendritic and axospinous symmetric synapses in the striatum (Roberts et al 1995).

It is possible that the increase in striatal volume of high-VCM rats is related to the reduction in the number of striatal inhibitory symmetric synapses and hypertrophied striatal mitochondrial profiles noted primarily in high-VCM rats compared to both drug-free and neuroleptic-treated low-VCM rats (Roberts et al 1995). Inhibitory synapses represent collaterals of inhibitory striatal projection neurons, terminals of striatal interneurons, and/or dopaminergic nigrostriatal afferents on the primary striatal neuron, the medium spiny neuron (Roberts et al 1995; DiFiglia 1987; DiFiglia and Aronis 1982; Somogyi et al 1981; Kubota et al 1987). Loss of inhibitory inputs to the striatal medium spiny neurons in high-VCM rats (Roberts et al 1995) could lead to a relative increase in excitatory tone on these neurons. This may have neurotrophic or growth-promoting effects (Fields and Nelson 1992), which

could result in larger striatal volumes in VCM-positive rats.

Enlarged mitochondria, which are predominantly seen in VCM-positive rats (Roberts et al 1995), may provide an alternative explanation for the increase in striatal volume seen in these rats. Enlarged mitochondria may reflect increased energy demands (Lehninger 1977) present in the striatum of VCM-positive rats. Swollen mitochondria may also reflect impaired energy metabolism (Bereiter-Hahn and Voth 1994) and an early event in neuronal injury that is not accompanied by other gross alterations in cell morphology (Isaev et al 1996; Saris and Eriksson 1995). More detailed studies of the relationship between these mitochondrial and striatal volume changes in VCM-positive rats should be pursued.

Implications for Patient Studies of the Effects of Chronic Antipsychotic Treatment on Striatal Volume

The finding of neuroleptic-induced striatal enlargement in this rat study is pertinent to longitudinal MRI studies of treated schizophrenic persons, since it supports the conclusion that chronic neuroleptic treatment can cause the striatal enlargement reported in human subject studies (Chakos et al 1994; Keshavan et al 1994). Replication of the finding in a postmortem animal model suggests that striatal enlargement in MRI scans of neuroleptic-treated patients is not due solely to increases in striatal blood flow and metabolism after neuroleptic treatment (Buchsbaum et al 1987). It also suggests that the striatal enlargement is not an artifact caused by an increase in the deposition of iron in the caudate nucleus (which has been reported in patients treated with neuroleptics, and which could alter the paramagnetic properties of caudate tissue and change MR signal intensity; Casanova et al 1992; Unger et al 1989).

There are parallels between the rat VCM syndrome and tardive dyskinesia (TD) in patients. In both the VCM syndrome in rats and TD in patients there is evidence for individual vulnerability to development of the movement disorder. Genetic vulnerability, age-related processes, and organic brain dysfunction may be factors contributing to intersubject variability in both chronically treated rats and patients (Tamminga et al 1990; Waddington et al 1986; Waddington 1990). Therefore, since neuroleptic-induced striatal enlargement in rats is associated with the high-VCM syndrome, striatal enlargement in schizophrenic patients who receive chronic neuroleptic treatment might be associated with a phase in the development of TD. Factors that might effect the relationship between striatal enlargement and TD might include genetic vulnerability, TD severity, chronicity of antipsychotic treatment, and age.

There is evidence that neuroleptic-induced striatal enlargement in human subjects may be reversed by treatment with clozapine. A recently published study of childhood-onset schizophrenia (Frazier et al 1996a) has replicated our previously reported finding (Chakos et al 1995) that clozapine reverses the striatal enlargement found in patients who had prior chronic neuroleptic treatment. We interpreted this as a withdrawal or normalizing effect due to clozapine's low D2 receptor affinity, rather than a drug-induced reduction in volume. Additional studies in the rat and in humans are needed to determine whether neuroleptic-induced striatal enlargement is reversed by drug withdrawal or by treatment with other atypical antipsychotics.

The functional significance of changes in striatal volume with neuroleptic treatment will depend on a better understanding of the functions and mechanisms of the striatum. Several investigators suggest that the neostriatum is involved in cognitive as well as motor functions (Unger et al 1989; Chakos et al 1995; Alexander et al 1990; Kolb 1977; Butters and Rosvold 1968; Aosaki et al 1994a, 1994b; Bereiter et al 1996; Rauch et al 1996). It is possible that neuroleptic-induced striatal volume changes play a role in the development of subtle cognitive impairment as well as the development of a movement disorder in vulnerable patients. An association between striatal enlargement and cognitive impairment has, in fact, been reported by Hokama et al (1995). These investigators reported striatal enlargement in patients who had a mean duration of illness of 15.7 years and had been prescribed neuroleptic medication throughout the entire course of illness, compared to controls. Striatal enlargement was associated with poorer neuropsychologic test performance on Hebb's Recurring Digits, a measure of the attention-related process of temporary memory storage, but not with performance on tests of long-term memory or abstraction (Hokama et al 1995).

Summary

This postmortem volumetric study in the rat supports the conclusion that the increase in striatal volume in first-episode schizophrenic patients who receive 12–18 months of neuroleptic treatment is an effect of the treatment (Chakos et al 1994; Keshavan et al 1994). The increase in striatal volume in rats is noted after 1 month of treatment and appears to be associated with the high-VCM syndrome. Possible determinants of this increase in volume may be the increases in striatal neuronal size and axon terminal size, which may reflect changes in the neuropil surrounding neuronal cell bodies in the corpus striatum. Additional determinants of the increase in striatal volume may be the hypertrophied striatal mitochondrial profiles

and reduction in inhibitory striatal symmetric synapses seen in high-VCM rats. More detailed studies of causal relationships of these possibilities should be pursued. In patients, the functional significance of neuroleptic-induced increases in striatal volumes is not clear. Longitudinal studies of schizophrenic patients on varying medication regimens and during drug-free periods will enable us to better understand the functional significance of and reversibility of medication-induced changes in striatal volume.

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