The Journal of Neuroscience, May 15, 1996, 16(10):3507–3510

The Vesicular Monoamine Transporter, in Contrast to the Dopamine Transporter, Is Not Altered by Chronic Cocaine Self-Administration in the Rat

Julie M. Wilson and Stephen J. Kish

Human Neurochemical Pathology Laboratory, Clarke Institute of Psychiatry, Toronto, Ontario, Canada M5T 1R8

Although much evidence suggests that the brain dopamine transporter (DAT) is susceptible to dopaminergic regulation, only limited information is available for the vesicular monoamine transporter (VMAT2). In the present investigation, we used a chronic, unlimited-access, cocaine self-administration paradigm to determine whether brain levels of VMAT2, as estimated using [^{3}H]dihydrotetrabenazine (DTBZ) binding, are altered by chronic exposure to a dopamine uptake blocker. Previously, we showed that striatal and nucleus accumbens DAT levels, as estimated by [^{3}H]WIN 35,428 and [^{3}H]GBR 12,935 binding, are altered markedly using this animal model (Wilson et al., 1994). However, in sequential sections from the same animals, [^{3}H]DTBZ binding was normal throughout the entire rostrocaudal extent of the basal ganglia (including striatum and nucleus accumbens), cerebral cortex, and diencephalon, as well as in midbrain and brainstem monoamine cell body regions, both on the last day of cocaine access and after 3 weeks of drug withdrawal. These data provide additional evidence that VMAT2, unlike DAT, is resistant to dopaminergic regulation.

Key words: cocaine; vesicular monoamine transporter; dihydrotetrabenazine; quantitative autoradiography; self-administration; unlimited access

In dopaminergic nerve terminals, dopamine is packaged into synaptic vesicles by the vesicular monoamine transporter (VMAT2). Synaptic vesicles exist in two functional pools: a releasable pool and a reserve pool (Greengard et al., 1993; Kelly, 1993). Vesicles in the releasable pool are held close to the plasma membrane, and upon depolarization of the nerve terminal, release dopamine into the synaptic cleft where it can interact with receptors to initiate a cellular response. The vesicles in the reserve pool, in contrast, are linked to the cytoskeleton and are recruited to the release pool to maintain the physiological requirements of the cell. Neurotransmission is terminated by the removal of dopamine from its site of action, mediated primarily through reuptake into the presynaptic nerve terminal via the plasma membrane dopamine transporter (DAT). Once inside the nerve terminal, dopamine can be stored in a cytoplasmic pool or packaged into synaptic vesicles via VMAT2. Both DAT and VMAT2 have been proposed as indices of presynaptic nerve terminal integrity. Radiotracers have been developed for imaging these sites using *in vitro* (ligand binding and autoradiography) and *in vivo* (positron emission tomography and single photon emission computerized tomography techniques) (Schoemaker et al., 1985; Scherman et al., 1988; Frost et al., 1993; Innes, 1994; Vander Borght et al., 1995).

Experimental evidence suggests that striatal and nucleus accumbens DAT levels, as estimated by radioligand binding techniques, can be altered markedly, independent of changes in dopamine nerve terminal density, to maintain normal synaptic dopamine levels. Although the data are not entirely consistent (see Wilson et al., 1994), striatal DAT concentrations can be elevated after administration of drugs that enhance synaptic dopamine levels (Weiner et al., 1989; Vander Borght et al., 1995) and reduced after administration of dopamine-depleting drugs (Kilbourn et al., 1992). Similarly, during chronic administration of the dopamine uptake blocker cocaine, which results in elevated synaptic dopamine levels (Pettit and Justice, 1991), DAT levels are increased (Alburges et al., 1993; Wilson et al., 1994), whereas during cocaine withdrawal, a state associated with subnormal synaptic dopamine concentrations (Parsons et al., 1991), DAT levels are reduced (Hitri et al., 1989; Sharpe et al., 1991; Farfel et al., 1992; Wilson et al., 1994). Although these data suggest that DAT is subject to dopaminergic regulation, the mechanism through which the regulatory changes are mediated remains to be determined. However, some evidence suggests the involvement of the dopamine D2 receptor in modulating DAT function (Cass and Gerhardt, 1994).

Only limited information is available with respect to the susceptibility of VMAT2 to dopaminergic regulation. Although two recent investigations have suggested that VMAT2 is not regulated readily by drugs that alter synaptic dopamine concentration or dopamine receptor function (Naudon et al., 1994; Vander Borght et al., 1995), these studies have been limited to short-term drug treatments (2 d and 2 weeks, respectively). Therefore, in the present investigation, we assessed whether binding of [^{3}H]dihydrotetrabenazine (DTBZ) to VMAT2 is altered after chronic (7 weeks) perturbation of the dopamine system with cocaine. An unlimited-access self-administration paradigm was used, in which rats received high doses of cocaine (~90 mg/kg per day). This paradigm has previously demonstrated marked up- and downregulation of the DAT during cocaine access and withdrawal, respectively (Wilson et al., 1994).

Received Jan. 23, 1996; revised Feb. 29, 1996; accepted March 4, 1996.

This study was supported by National Institutes of Health NIDA DA07182 (S.J.K.). J.M.W. is the recipient of a Commonwealth Scholarship Award.

Correspondence should be addressed to Dr. Stephen J. Kish, Human Neurochemical Pathology Laboratory, Clarke Institute of Psychiatry, 250 College Street, Toronto, Ontario, Canada M5T 1R8.

MATERIALS AND METHODS

An unlimited cocaine self-administration paradigm was used to investigate the influence of prolonged, high-dose cocaine exposure on VMAT2. The results presented here were obtained from sequential brain sections from the same animals used in a previous investigation, in which [^{3}H]WIN 35,428 and [^{3}H]GBR 12,935 binding to the DAT was measured, and in which the self-administration paradigm has been described in detail (Wilson et al., 1994). Briefly, male Wistar rats (350 to 400 gm) were implanted with chronic indwelling jugular vein catheters and allowed to recover from surgery for 24–48 hr. The rats lived in their operant chambers for the duration of the experiment. The chambers contained two response levers, a food receptacle, and a standard water bottle. A stimulus light was mounted above each lever and was illuminated for the duration of an infusion (3–4 sec) after a response was made. Infusion pumps were located outside sound-attenuating wooden enclosures. One to 2 d after surgery, the drug-naive rats, with no previous experience in the operant chamber, were given unlimited access to cocaine self-administration. Daily sessions began at 10:00 A.M. and lasted 24 hr/d for at least 3 weeks (mean self-administration period = 7 weeks ± 5 d). Cocaine (0.1 mg per infusion) was delivered after a response on the left lever, and the dose was controlled by the duration of infusion (1 sec per 100 gm body weight). Food intake was limited to 20 gm/d during the self-administration period. Because the experimental chamber acts as the home environment for the self-administering animals, control animals (n = 15, age- and food-matched) remained in their home cages throughout.

One group of rats (on-cocaine group, n = 10) was killed on the last day of cocaine access with no withdrawal from cocaine. The maximal interval between the last cocaine infusion and death was 4 hr. A second group (cocaine-withdrawn group, n = 8) was killed after a 3 week withdrawal period. Rats were killed by decapitation and the brain removed rapidly and divided longitudinally into two halves. One half was frozen immediately over dry ice and stored at −80°C until cryostat sectioning. Serial coronal sections (20 μm) were cut at −20°C, thaw mounted onto gelatin-coated slides, and stored at −80°C until assayed. The second half was dissected over a cold plate into discrete brain areas that were stored at −80°C and retained for measurement of monoamines and metabolites (Wilson et al., 1994).

Binding of [^{3}H]DTBZ to the vesicular monoamine transporter was assessed using minor modifications of the procedure of Rostène and colleagues (1992). Brain sections were preincubated for 20 min at 25°C in 50 mM sodium phosphate buffer, pH 7.7, to remove any residual cocaine that might be present, then incubated for 40 min in the same buffer containing 5 nM [^{3}H]DTBZ (155 Ci/mmol, Amersham, Oakville, Ontario, Canada) in the presence (nonspecific binding) or absence (total binding) of 2 μM tetrabenazine. The concentration of [^{3}H]DTBZ was equal to the equilibrium dissociation constant (K_d) for [^{3}H]DTBZ binding in rat striatum (Darchen et al., 1989) and was chosen to permit detection of changes in both affinity (K_d) and density (B_{max}) of VMAT2. Sections were washed twice in buffer at 0–4°C for 3 min and rinsed in distilled water before drying. Dried sections were apposed to tritium-sensitive film (Eastman Kodak Hyperfilm, Rochester, NY) at 0–4°C for 2 weeks in the presence of tritium-calibrated ^{14}C-labeled standards. Films were developed using Kodak D19 developer, and densitrometric analysis of autoradiograms was performed using a camera-based computerized imaging device (MCID, Imaging Research, St. Catharines, Ontario, Canada).

As described in detail previously (Wilson et al., 1994), brain areas were subdivided in anterior-posterior, dorsoventral, and mediolateral planes where appropriate.

RESULTS

Cocaine self-administration

The mean daily cocaine intake in rats given unlimited access to self-administration of cocaine was 36.8 ± 4.2 mg/d (~90 mg/kg per day). There were no statistically significant differences (using an unpaired Student's t test) in mean daily cocaine intake between the on-cocaine (42 ± 4 mg) and cocaine-withdrawn (30 ± 8 mg) groups. In addition, there were no significant differences between total cocaine intake (on-cocaine, 1700 ± 290 mg; cocaine-withdrawn, 1690 ± 350 mg; $p > 0.05$), maximum daily intake (on-cocaine, 132 ± 18 mg; cocaine-withdrawn, 111 ± 26 mg; $p > 0.05$), or duration of access (on cocaine, 41 ± 6 d; cocaine-withdrawn, 60 ± 7 d; $p > 0.05$) between the on-cocaine and cocaine-withdrawn groups. The daily patterns of cocaine intake have been described previously (Wilson et al., 1994).

Vesicular monoamine transporter distribution in control brain

Specific [^{3}H]DTBZ binding was detected in dopamine (striatum, nucleus accumbens, olfactory tubercle, substantia nigra, ventral tegmental area), noradrenaline (hypothalamus, septum, locus coeruleus), and serotonin (dorsal raphe) brain areas (Table 1). The highest density of [^{3}H]DTBZ binding was in the basal ganglia (striatum, nucleus accumbens) and olfactory tubercle. Subregional analysis of the binding data revealed a heterogeneous pattern of binding in dopaminergic nerve terminal areas, with rostrocaudal and mediolateral gradients being evident in striatum. Thus, [^{3}H]DTBZ binding was more dense in the anterior than posterior regions of the striatum (rostral pole, 257 pmol/μg tissue; caudal body, 180 pmol/μg tissue) and nucleus accumbens (anterior, 254 pmol/μg tissue; posterior, 223 pmol/μg tissue). The rostral pole and rostral body of the striatum displayed a slight decreasing mediolateral gradient, although this was reversed in intermediate striatum, with the lateral portion displaying the highest density of binding. Dorsoventral gradients were evident only in the caudal body of the striatum in which the ventral subdivision showed the highest binding (ventral, 248 pmol/μg tissue; dorsal 128 pmol/μg tissue).

Vesicular monoamine transporter distribution in cocaine exposed brain

No significant changes in [^{3}H]DTBZ binding to the VMAT2 were detected in any brain area after chronic cocaine self-administration, either on the last day of cocaine access or after 3 weeks of drug withdrawal (Table 1). In contrast, levels of DAT (as assessed using [^{3}H]WIN 35,428 and [^{3}H]GBR 12,935 binding) in striatum and nucleus accumbens were up- and downregulated during cocaine access and withdrawal, respectively (Fig. 1) (see Wilson et al., 1994).

DISCUSSION

VMAT2 in normal rat brain

The distribution of [^{3}H]DTBZ binding correlated with monoaminergic-rich brain areas, as described previously (Scherman, 1986; Scherman et al., 1986; Scherman et al., 1988; Darchen et al., 1989; Rostene et al., 1992). The highest density of [^{3}H]DTBZ binding was in the dopamine-rich areas of striatum, nucleus accumbens, and olfactory tubercle. Lesions of the nigrostriatal pathway with 6-hydroxydopamine result in a marked depletion of [^{3}H]DTBZ binding sites in rat striatum (Darchen et al., 1989; Masuo et al., 1990), together with reduced tyrosine hydroxylase activity (Masuo et al., 1990), suggesting that a substantial proportion (~95%) of striatal [^{3}H]DTBZ binding is to dopaminergic nerve terminals (Masuo et al., 1990). Based on the relative concentrations of dopamine and serotonin in striatum, it generally is assumed that only ~5% of monoaminergic neurons in the striatum are serotonergic (Scherman et al., 1986).

The subregional distribution of [^{3}H]DTBZ binding revealed a heterogeneous pattern of binding in dopaminergic nerve terminal areas. The rostrocaudal gradient observed for [^{3}H]DTBZ binding in the striatum was similar to that reported previously for [^{3}H]GBR 12,935 and [^{3}H]WIN 35,428 binding (Wilson et al., 1994), with the highest density observed in the rostral body. Similarly, a clear dorsoventral gradient was observed for all three

Table 1. [^{3}H]DTBZ binding in rat brain: influence of chronic unlimited access to self-administration of cocaine

Brain region	Control	On-cocaine	Withdrawn
Cortex			
Frontal	12.7 ± 0.2	9.0 ± 0.7	8.1 ± 1.1
Cingulate	12.2 ± 0.7	13.5 ± 1.1	12.5 ± 1.3
Limbic	20.4 ± 0.9	21.7 ± 1.6	18.7 ± 2.0
Occipital	5.2 ± 0.2	5.3 ± 0.8	3.9 ± 0.8
Basal ganglia			
Nucleus accumbens			
Whole	240 ± 5	231 ± 10	224 ± 10
Anterior	254 ± 6	234 ± 8	233 ± 12
Posterior	224 ± 3	226 ± 14	218 ± 9
Striatum			
Whole	202 ± 2	198 ± 9	191 ± 10
Rostral pole	257 ± 10	227 ± 16	229 ± 12
Dorsomedial	266 ± 15	228 ± 26	235 ± 19
Dorsolateral	248 ± 9	213 ± 14	235 ± 14
Ventromedial	273 ± 10	260 ± 11	241 ± 16
Ventrolateral	225 ± 11	206 ± 13	201 ± 12
Rostral body	238 ± 5	233 ± 14	231 ± 10
Dorsomedial	248 ± 9	250 ± 18	249 ± 10
Dorsointermed.	232 ± 6	241 ± 15	227 ± 11
Dorsolateral	229 ± 8	223 ± 11	220 ± 8
Intermed.-medial	265 ± 8	254 ± 16	262 ± 12
Intermed.-intermed.	215 ± 6	210 ± 12	203 ± 11
Intermed.-lateral	209 ± 7	203 ± 10	198 ± 12
Ventromedial	266 ± 7	251 ± 16	258 ± 12
Ventrointermed.	245 ± 6	239 ± 16	236 ± 11
Ventrolateral	238 ± 5	228 ± 15	226 ± 13
Intermediate body	199 ± 4	209 ± 12	194 ± 12
Dorsomedial	202 ± 8	230 ± 16	211 ± 14
Dorsointermed.	188 ± 6	199 ± 15	182 ± 13
Dorsolateral	212 ± 9	212 ± 9	194 ± 15
Intermed.-medial	174 ± 6	186 ± 16	175 ± 14
Intermed.-intermed.	169 ± 3	173 ± 11	158 ± 10
Intermed.-lateral	212 ± 7	212 ± 6	187 ± 10
Ventromedial	169 ± 7	164 ± 11	163 ± 10
Ventrointermed.	218 ± 6	221 ± 10	209 ± 11
Ventrolateral	256 ± 7	257 ± 9	233 ± 15
Caudal body	179 ± 3	174 ± 6	168 ± 10
Dorsal	129 ± 5	132 ± 7	130 ± 10
Intermed.	170 ± 4	162 ± 6	156 ± 11
Ventral	248 ± 7	235 ± 9	227 ± 13
Caudate tail	112 ± 5	109 ± 8	97 ± 7
Bed nucleus of stria terminalis			
Anterior	89 ± 5	80 ± 6	93 ± 7
Ventral	148 ± 9	145 ± 10	130 ± 11
Fundus striati	221 ± 6	187 ± 24	195 ± 19
Globus pallidus	11.7 ± 0.8	11.8 ± 1.0	9.8 ± 1.6
Basal forebrain			
Olfactory tubercle			
Whole	192 ± 5	182 ± 5	185 ± 5
Anterior	192 ± 6	183 ± 4	185 ± 6
Posterior	188 ± 7	181 ± 8	182 ± 4
Lateral septum			
Dorsal	208 ± 7	256 ± 19	239 ± 9
Intermed.	58 ± 3	78 ± 10	69 ± 6
Ventral	172 ± 6	196 ± 19	191 ± 13
Medial septum	47 ± 5	49 ± 6	45 ± 8
Pyramidal cell layer	22 ± 1	25 ± 2	22 ± 3
Hippocampus	12 ± 1	14 ± 1	12 ± 1
Basolateral amygdala	51 ± 2	54 ± 3	48 ± 3
Diencephalon			
Suprachiasmatic nucleus	89 ± 14	80 ± 9	57 ± 14
Supraoptic nucleus	145 ± 9	151 ± 10	167 ± 11
Paraventricular nucleus	150 ± 8	183 ± 14	160 ± 13
Hypothalamus			
Anterior	61 ± 3	76 ± 4	62 ± 4
Dorsomedial	79 ± 7	83 ± 5	79 ± 8
Ventromedial	57 ± 3	56 ± 4	58 ± 3
Lateral preoptic area	51 ± 3	54 ± 6	53 ± 5
Medial preoptic area	80 ± 3	88 ± 3	77 ± 6
Habenula			
Medial	28 ± 2	31 ± 4	30 ± 3
Lateral	16 ± 5	11 ± 2	15 ± 4
Thalamus			
Anteroventral thalamic nucleus	55 ± 3	51 ± 3	54 ± 5
Paratenial thalamic nucleus	74 ± 9	72 ± 11	75 ± 7
Paraventricular thalamic nucleus	88 ± 6	87 ± 7	100 ± 12
Midbrain			
Substantia nigra	92 ± 8	82 ± 5	81 ± 7
Ventral tegmental area	101 ± 5	94 ± 6	91 ± 8
Superior colliculus	27 ± 1	29 ± 2	25 ± 2
Periaqueductal grey	33 ± 2	37 ± 3	34 ± 4
Medial raphe	56 ± 14	43 ± 12	61 ± 13
Dorsal raphe	144 ± 12	148 ± 11	140 ± 21
Subincertal nucleus	55 ± 3	51 ± 4	44 ± 3
Brainstem			
Locus coeruleus	174 ± 39	267 ± 23	209 ± 47

Data are subregional distribution (mean ± SEM; pmol/μg tissue) of [^{3}H]DTBZ binding in brain of control rats (n = 15) and of rats killed on the last day of (n = 10) or 3 weeks after withdrawal from (n = 8) chronic, unlimited access to self-administration of cocaine.

ligands in the caudal body of the striatum, with the highest binding density detected in the ventral subdivision. Previously we have reported differential localization of [^{3}H]GBR 12,935 and [^{3}H]WIN 35,428 binding sites (highest density in dorsomedial and ventrolateral subdivisions, respectively) in the rostral body of the striatum (Wilson et al., 1994), suggesting that these ligands might bind to different affinity states or variants of the DAT. The density gradients observed for [^{3}H]DTBZ binding in the striatum could reflect a composite of [^{3}H]GBR 12,935 and [^{3}H]WIN 35,428 binding sites, suggesting that [^{3}H]DTBZ binds to all dopaminergic nerve terminals, irrespective of the expressed form of DAT.

Although [^{3}H]DTBZ binding is predominantly to dopaminergic nerve terminals in the basal ganglia, significant binding, as expected, was detected in other brain areas that contain noradrenergic and serotonergic innervation (hypothalamus, septum), as well as in the corresponding cell body areas (locus coeruleus and raphe nuclei).

Cocaine and the vesicular monoamine transporter

The present results demonstrate that [^{3}H]DTBZ binding in rat brain was unaltered after chronic, unlimited access to self-administration of high doses (~90 mg/kg per day) of cocaine, both on the last day of cocaine access and after a 3 week withdrawal period. These findings are consistent with the recent demonstration from two independent studies (Naudon et al., 1994; Vander Borght et al., 1995) that pharmacological agents that modify synaptic dopamine concentration (mazindol, deprenyl, L-dopa) or dopamine receptor function (haloperidol, bromocriptine, apomorphine) do not alter brain VMAT2 concentration. This is in contrast to DAT, which undergoes marked up- and downregulation after administration of drugs that enhance (Weiner et al., 1989; Vander Borght et al., 1995) and reduce (Kilbourn et al., 1992), respectively, synaptic dopamine concentrations. Thus, whereas DAT regulation might reflect a compensatory change to modify synaptic dopamine concentrations and to maintain dopaminergic neurotransmission at more normal levels, VMAT2 appears to be highly resistant to such compensatory changes.

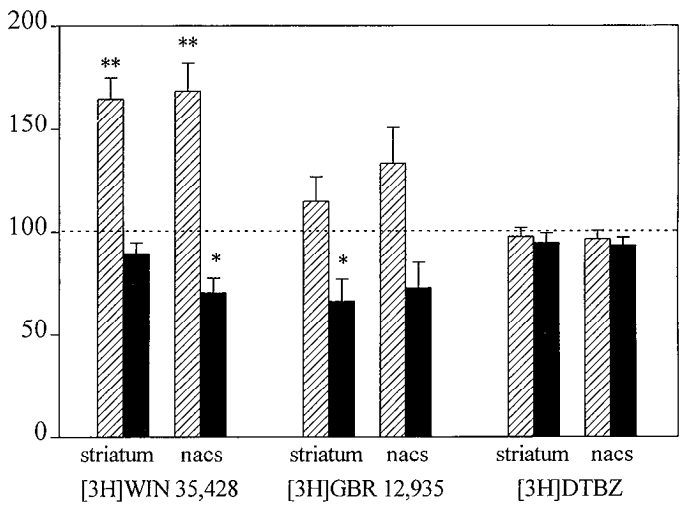

Figure 1. Bars represent [^{3}H]WIN 35,428, [^{3}H]GBR 12,935, and [^{3}H]DTBZ binding (expressed as a percentage of control, n = 15) in striatum and nucleus accumbens (nacs) of rats exposed to unlimited-access cocaine self-administration and killed on the last day of cocaine access (n = 10) (*hatched bars*) or 3 weeks after drug withdrawal (n = 8) (*black bars*). One-way ANOVA, followed by Fisher's least significant difference test (*asterisk* indicates $p < 0.05$; *double asterisk* indicates $p < 0.001$). Data for [^{3}H]WIN 35,428 and [^{3}H]GBR 12,935 bindings are taken from Wilson et al. (1994).

However, although these data suggest that there is no change in the total number of synaptic monoamine-containing vesicles, it is unknown whether the proportion of releasable versus reserve pools of vesicles (for review, see Greengard et al., 1993) are altered. In this regard, it is conceivable that the efficiency of dopaminergic neurotransmission could be modulated by a shift in the relative number of synaptic vesicles available at the plasma membrane for exocytosis, without the need for alterations in vesicle synthesis or degradation (cf. Greengard et al., 1993).

In conclusion, the present data provide additional support to the suggestion that total VMAT2 levels are not readily susceptible to dopaminergic regulation. Consequently, measurement of the [^{3}H]DTBZ binding site on VMAT2 might provide an objective estimate of monoaminergic nerve terminal integrity (Vander Borght et al., 1995). In this regard, the present data are consistent with those from other investigations (Ryan et al., 1988; Seiden and Kleven, 1988; Bennet et al., 1993a,b), which suggest that chronic cocaine exposure is not associated with actual loss of dopaminergic nerve terminals in rat brain.

REFERENCES

Alburges ME, Narang N, Wamsley JK (1993) Alterations in the dopaminergic receptor system after chronic administration of cocaine. Synapse 14:314–323.

Bennett BA, Hyde CE, Pecora JR, Clodfelter JE (1993a) Long-term cocaine administration is not neurotoxic to cultured fetal mesencephalic dopamine neurons. Neurosci Lett 153:210–214.

Bennett BA, Hyde CE, Pecora JR, Clodfelter JE (1993b) Differing neurotoxic potencies of methamphetamine, mazindol, and cocaine in mesencephalic cultures. J Neurochem 60:1444–1452.

Cass WA, Gerhardt GA (1994) Direct *in vivo* evidence that D2 dopamine receptors can modulate dopamine uptake. Neurosci Lett 176:259–263.

Darchen F, Masuo Y, Vial M, Rostene W, Scherman D (1989) Quantitative autoradiography of the rat brain vesicular monoamine transporter using the binding of [^{3}H]dihydrotetrabenazine and 7-amino-8-[^{125}I]iodoketanserin. Neuroscience 33:341–349.

Farfel GM, Kleven MS, Woolverton WL, Seiden LS, Perry BD (1992) Effects of repeated injections of cocaine on catecholamine receptor binding sites, dopamine transporter binding sites and behavior in Rhesus monkeys. Brain Res 578:235–243.

Frost JJ, Rosier AJ, Reich SG, Smith JS, Ehlers MD, Snyder SH, Ravert HT, Dannals RF (1993) Positron emission tomographic imaging of the dopamine transporter with ^{11}C-WIN 35,428 reveals marked declines in mild Parkinson's disease. Ann Neurol 34:423–431.

Greengard P, Valtorta F, Czernik AJ, Benfenati F (1993) Synaptic vesicle phosphoproteins and regulation of synaptic function. Science 259:780–785.

Hitri A, Suddath RL, Wyatt RJ (1989) Effect of cocaine withdrawal on dopamine uptake sites in the rat frontal cortex. Biol Psychiatry 25:48A.

Innes RB (1994) Single-photon emission tomography imaging of dopamine terminal innervation: a potential clinical tool in Parkinson's disease. Eur J Nucl Med 21:1–5.

Kelly RB (1993) Storage and release of neurotransmitters. Neuron [Suppl] 10:43–53.

Kilbourn MR, Sherman PS, Pisan T (1992) Repeated reserpine administration reduces *in vivo* [^{18}F]GBR 13119 binding to the dopamine uptake site. Eur J Pharmacol 216:109–112.

Masuo Y, Pélaprat D, Scherman D, Rostène W (1990) [^{3}H]dihydrotetrabenazine, a new marker for the visualisation of dopaminergic denervation in the rat striatum. Neurosci Lett 114:45–50.

Naudon L, Leroux-Nicollet I, Costentin J (1994) Short-term treatments with haloperidol or bromocriptine do not alter the density of the monoamine vesicular transporter in the substantia nigra. Neurosci Lett 173:1–4.

Parsons LH, Smith AD, Justice Jr JB (1991) Basal extracellular dopamine is decreased in the rat nucleus accumbens during abstinence from chronic cocaine. Synapse 9:60–65.

Pettit HO, Justice Jr JB (1991) Effect of dose on cocaine self-administration behavior and dopamine levels in the nucleus accumbens. Brain Res 539:94–102.

Rostène W, Boja JW, Scherman D, Carrol FI, Kuhar MJ (1992) Dopamine transport: pharmacological distinction between the synaptic membrane and the vesicular transporter in rat striatum. Eur J Pharmacol 218:175–177.

Ryan LJ, Martone ME, Linder JC, Groves PM (1988) Cocaine, in contrast to D-amphetamine, does not cause axonal terminal degeneration in neostriatum and agranular frontal cortex of Long–Evans rats. Life Sci 43:1403–1409.

Scherman D (1986) Dihydrotetrabenazine binding and monoamine uptake in mouse brain regions. J Neurochem 47:331–339.

Scherman D, Boschi G, Rips R, Henry JP (1986) The regionalization of [^{3}H]dihydrotetrabenazine binding sites in mouse brain and its relationship to the distribution of monoamines and their metabolites. Brain Res 370:176–181.

Scherman D, Raisman R, Ploska A, Agid Y (1988) [^{3}H]dihydrotetrabenazine, a new in vitro monoaminergic probe for human brain. J Neurochem 50:1131–1136.

Schoemaker H, Pimoule C, Arbilla S, Scatton B, Javoy-Agid F, Langer SZ (1985) Sodium-dependent [^{3}H]cocaine binding associated with dopamine uptake sites in the rat striatum and human putamen decrease after dopaminergic denervation and in Parkinson's disease. Naunyn Schmiedebergs Arch Pharmacol 329:227–235.

Seiden LS, Kleven MS (1988) Lack of toxic effects of cocaine on dopamine or serotonin neurons in the rat brain. In: Mechanisms of cocaine abuse and toxicity, pp 276–289. Washington, DC: NIDA Research Monograph Series, U.S. Department Health and Human Services.

Sharpe LG, Pilotte NS, Mitchell WM, De Souza EB (1991) Withdrawal of repeated cocaine decreases autoradiographic [^{3}H]mazindol-labelling of dopamine transporter in rat nucleus accumbens. Eur J Pharmacol 203:141–144.

Vander Borght T, Kilbourn M, Desmond T, Kuhl D, Frey K (1995) The vesicular monoamine transporter is not regulated by dopaminergic drug treatments. Eur J Pharmacol 294:577–583.

Weiner HL, Hashim A, Lajtha A, Sershen H (1989) Chronic L-deprenyl-induced up-regulation of the dopamine uptake carrier. Eur J Pharmacol 163:191–194.

Wilson JM, Nobrega JN, Carroll ME, Niznik HB, Shannak K, Lac ST, Pristupa ZB, Dixon LM, Kish SJ (1994) Heterogeneous subregional binding patterns of ^{3}H-WIN 35,428 and ^{3}H-GBR 12,935 are differentially regulated by chronic cocaine self-administration. J Neurosci 14: 2966–2979.