Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 479 (2003) 283–289
www.elsevier.com/locate/ejphar

Impact of psychostimulants on vesicular monoamine transporter function

Annette E. Fleckenstein*, Glen R. Hanson

Department of Pharmacology and Toxicology, University of Utah, 30 South 2000 East, Room 201, Salt Lake City, UT 84112, USA

Accepted 21 August 2003

Abstract

The vesicular monoamine transporter-2 (VMAT-2) facilitates the sequestration of catecholamines and serotonin into synaptic vesicles, and is therefore an essential regulator of monoaminergic neuronal function. VMAT-2 proteins may also play a role in neuroprotection, since these transporters have the capacity to sequester neurotoxins within vesicles. Recent studies have demonstrated that psychostimulants, particularly dopamine ''releasers'' and ''reuptake inhibitors'', differentially alter VMAT-2 function. As described in this review, these studies not only provide insight into the pharmacological actions of stimulants, but also mechanisms underlying neurodegenerative disorders, including Parkinson's disease.

Keywords: Vesicular monoamine transporter; Amphetamine; Methylphenidate; Cocaine

1. Overview

The vesicular monoamine transporter-2 (VMAT2) utilizes proton electrochemical gradients to transport monoamines into vesicles in preparation for exocytotic release. It contains 12 putative transmembrane domains (Erickson et al., 1992), and is potently inhibited by reserpine and tetrabenazine. VMAT-2 protein is associated with both small synaptic vesicles and large dense core vesicles, at least in rat solitary nuclei (Nirenberg et al., 1995).

Many investigators utilize the presence of VMAT-2 as a marker of neurotoxicity and/or neurodegeneration since a loss of catecholaminergic or serotonergic neurons predictably decreases VMAT-2 levels. For example, in Parkinson's disease, a reduction in binding of the VMAT-2 ligand, dihydrotetrabenazine, accompanies dopaminergic degeneration (Frey et al., 1996; Thibaut et al., 1995; Lehericy et al., 1994). Accordingly, administration of a high-dose regimen of the psychostimulant, methamphetamine, damages dopaminergic nerve terminals and reduces dihydrotetrabenazine binding in rodent striata days after treatment (Hogan et al., 2000). Similarly, in vervet monkeys, repeated methamphetamine injections decrease VMAT-2 immunoreactivity as assessed 1 week after treatment (Harvey et al., 2000). Interestingly, no changes in VMAT-2 levels were found in chronic human methamphetamine abusers despite reduced levels of three dopamine nerve terminal markers (dopamine, tyrosine hydroxylase and the dopamine transporter) in postmortem striatum (Wilson et al., 1996a). These and other studies demonstrate that assessment of VMAT-2 levels can provide valuable insights into the persistent impact of psychostimulant treatment.

2. Amphetamine analogs acutely alter VMAT-2 function

In addition to persistent effects, amphetamine and its analogs rapidly alter VMAT-2 function. Amphetamine is a weak base substrate for monoamine transporters, including the dopamine transporter. In addition, it is highly lipophilic and readily enters nerve terminals by diffusing across plasmalemmal membranes. Once inside, amphetamine purportedly depletes vesicular monoamine stores by several mechanisms: first, it binds directly, albeit with low affinity, to VMAT-2 (as assessed in cos cells transfected with human VMAT) and thereby inhibits vesicular uptake (Gonzalez et al., 1994). Second, amphetamine, a weak base, diffuses across vesicle membranes in its uncharged form where it accumulates in its charged form as a result of the lower pH in the synaptic vesicle interior. As vesicular amphetamine concentrations increase, the buffering capacity of the vesicle is lost resulting in a diminished pH gradient (Sulzer and

* Corresponding author. Tel.: +1-801-585-7474; fax: +1-801-585-5111.
E-mail address: fleckenstein@hsc.utah.edu (A.E. Fleckenstein).

0014-2999/$ - see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2003.08.077

Rayport, 1990; Sulzer et al., 1993, 1995) and thereby a loss of free energy necessary for monoamine sequestration (Johnson, 1988). This results in reduced vesicular monoamine uptake. In addition, the collapse of the gradient purportedly results in competition for protons between the monoamines and amphetamine, and increases uncharged vesicular neurotransmitter concentrations that diffuse out of vesicles along a concentration gradient (Sulzer and Rayport, 1990).

A predictable consequence of diminished vesicular dopamine sequestration would be that amphetamine reduces the number of dopamine molecules released per vesicle: this finding has been reported in studies employing invertebrate neurons (Anderson et al., 1998) and PC12 cells (Sulzer et al., 1995). Consonant with a vesicle-depleting action, amphetamine application decreases the dopamine available for depolarization-evoked release (Jones et al., 1998).

Concurrent with depleting vesicular dopamine content, amphetamine purportedly increases cytoplasmic dopamine concentrations. The stimulant and its derivatives promote nonvesicular dopamine efflux by reverse transport through the plasmalemmal dopamine transporter (Fischer and Cho, 1979; Raiteri et al., 1979; Liang and Rutledge, 1982; Sulzer et al., 1993, 1995; Jones et al., 1998).

In addition to disrupting the proton gradient and thereby dopamine sequestration, recent ex vivo studies have demonstrated that amphetamine analogs rapidly decrease vesicular dopamine transport through a mechanism involving a redistribution of VMAT-2 protein, and presumably associated vesicles. Specifically, striatal tissues were obtained from saline- and methamphetamine-treated rats, and subjected to biochemical fractionation as described by Brown et al. (2000) and Riddle et al., 2002. This protocol separated tissues into several fractions, including a whole synaptosomal fraction, a synaptic vesicle-enriched (non-membrane-associated) fraction, and a plasmalemmal membrane-associated fraction. Using this protocol, it was observed that a single methamphetamine injection rapidly (within 1 h) and reversibly decreases dopamine uptake in a vesicle-enriched fraction obtained from rat striata; an effect that was not due to residual methamphetamine introduced by the original injections (Brown et al., 2002). This effect was largely associated with dopaminergic nerve terminals, since destruction of the striatal serotonergic projections did not alter vesicular dopamine uptake in this preparation (Brown et al., 2000). The decrease in vesicular dopamine uptake caused by a single methamphetamine administration was attenuated by pretreatment with the dopamine D2 antagonist, eticlopride, but not the dopamine D1, antagonist, SCH23390 (Brown et al., 2002), suggesting that activation of D2 receptors contributes to this phenomenon. Other studies have suggested that amphetamine may inhibit dopamine release by activating D2 autoreceptors indirectly (Schmitz et al., 2001) However, as described below, the role of D2 receptors in regulating VMAT-2 and vesicular dopamine release is complex and is the focus of ongoing studies.

Concurrent with the publication by Brown et al. (2000) was the report by Hogan et al. (2000) that multiple high-dose injections of methamphetamine decreased vesicular dopamine transport and binding of dihydrotetrabenazine as assessed 1 day after treatment in purified striatal vesicles of mice. Importantly, these investigators also found that total dihydrotetrabenazine binding in whole mouse striatal homogenates was not affected at this 1 day time point. These data allowed for the possibility that VMAT-2 protein was redistributed within nerve terminals after methamphetamine treatment. Consistent with a redistribution hypothesis, Riddle et al. (2002) reported multiple high-dose methamphetamine injections rapidly (within 1 h) redistribute rat striatal VMAT-2 immunoreactivity from synaptic vesicle-enriched fractions to, at high doses, a location not retained in the preparation of the synaptosomes; an effect not likely attributable to an overall loss of VMAT-2 protein.

The methamphetamine-induced decrease in vesicular dopamine uptake appears common among dopamine "releasing agents". For instance, a single administration of amphetamine per se rapidly and reversibly decreases vesicular dopamine uptake (Riddle et al., in press). Administration of methylenedioxymethamphetamine rapidly decreases striatal vesicular dopamine transport as well. Unlike effects of multiple methamphetamine injections, the methylenedioxymethamphetamine-induced decrease partially recovers by 24 h after drug treatment. D2 dopamine receptors contribute to this methylenedioxymethamphetamine-induced deficit, as the phenomenon was attenuated by pretreatment with eticlopride (Hansen et al., 2002).

A methamphetamine-related redistribution of vesicles and/or disruption of dopamine sequestration may have important implications regarding the neurotoxic properties of the stimulant (see Fleckenstein et al., 2000). It is well established that high-dose methamphetamine treatment causes persistent deficits in dopaminergic neuronal function in rodents (Hotchkiss et al., 1979; Hotchkiss and Gibb, 1980; Wagner et al., 1980; Ricaurte et al., 1982), non-human primates (Woolverton et al., 1989) and humans (Wilson et al., 1996a). Several groups have suggested that dopamine, per se, contributes to this long-term damage, as it is attenuated by pretreatment of rats with the dopamine synthesis inhibitor, α-methyl-*p*-tyrosine (Gibb and Kogan, 1979; Wagner et al., 1983; Schmidt et al., 1985). The precise mechanism whereby dopamine contributes to these long-term decreases is unknown, although dopamine can contribute to the formation of neurotoxic reactive species (Graham et al., 1978; Hastings, 1995). Since cytoplasmic dopamine levels are regulated largely by the VMAT-2, deficits in the function of this carrier protein may contribute to the damage. Specifically, by decreasing vesicular dopamine uptake, it may accumulate within nerve terminals promoting the formation of reactive species and thereby causing neuronal damage.

Support for the hypothesis that disruption of dopamine sequestration contributes to methamphetamine-induced dopaminergic deficits comes from findings of Fumagalli et al.

(1999) that in VMAT-2 heterologous knockout mice, methamphetamine-induced deficits are enhanced compared to corresponding wild-type mice. Furthermore, methamphetamine-induced degeneration of dopamine neurites and accumulation of metabolites of oxidized dopamine vary inversely with VMAT-2 expression in postnatal ventral midbrain neuronal cultures derived from VMAT-2 knockout mice (Larsen et al., 2002). Further support for this possibility comes from findings that there is decreased vesicular dopamine content in vesicles purified from the striata of rats treated with methamphetamine (Sandoval et al., 2003). This phenomenon likely results from altered trafficking of VMAT-2, in addition to the direct inhibition of VMAT-2 and the weak base disruption of the pH gradient necessary for vesicular uptake as described above. Regardless of the process, the decrease in sequestered dopamine caused by methamphetamine treatment presumably increases cytoplasmic dopamine concentrations and perhaps reactive oxygen species formation.

Of interest are recent findings that pretreatment of rats with an escalating dose-paradigm of methamphetamine attenuates not only the persistent dopaminergic deficits caused by a subsequent high-dose methamphetamine "challenge" administration, but also the acute decrease in vesicular dopamine uptake caused by the challenge. Neither attenuation was due to differences in pharmacokinetics effected by the methamphetamine-pretreatment paradigm (Johnson-Davis et al., 2003). These data support the possibility of a causal link between the acute redistribution of VMAT-2 and the persistent dopaminergic deficits caused by the stimulant.

3. Plasmalemmal dopamine reuptake inhibitors and releasers differentially alter VMAT-2 function

Relatively few studies have assessed the impact of plasmalemmal dopamine reuptake inhibitors and releasers on VMAT-2. Among the few reports include the observation by some (Wilson et al., 1996b; Little et al., 2003), but not all (Staley et al., 1997), investigators that human cocaine users have less VMAT2 protein: whether this represents damage to aminergic neurons or an adaptive response to chronic cocaine use warrants investigation.

In contrast to these studies assessing the long-term impact of cocaine, the acute action of this stimulant on VMAT-2 has been recently investigated. It was reported that administration of reuptake inhibitors to rats abruptly (within 1 h) and reversibly increases both dopamine uptake and dihydrotetrabenazine binding, as assessed ex vivo in a vesicle-enriched fraction prepared according to protocol by Brown et al. (2000) described above. More selective inhibitors of the dopamine transporters (GBR12935 and amfonelic acid), but not the plasmalemmal serotonin transporter (fluoxetine), also increase vesicular dopamine uptake (Brown et al., 2001). The cocaine-induced increase in uptake corresponds to a shift in VMAT-2 protein from a plasmalemmal membrane-associated to a synaptic vesicle-enriched compartment (Riddle et al., 2002).

Subsequent studies have demonstrated that administration of the dopamine D2 antagonist, eticlopride, but not SCH23390 inhibits the cocaine-induced increases in dopamine uptake in purified vesicular preparations. Similar to the effects of cocaine, treatment with the dopamine D2 agonist, quinpirole, increases both vesicular dopamine uptake and dihydrotetrabenazine binding. In contrast, administration of the dopamine D1 agonist, SKF81297, is without effect on vesicular dopamine uptake or dihydrotetrabenazine binding. Finally, co-administration of quinpirole and cocaine does not further increase vesicular dopamine uptake or dihydrotetrabenazine binding when compared to treatment with either agent alone. These data suggest that cocaine-induced increases in vesicular dopamine uptake and dihydrotetrabenazine binding are due to a D2 receptor-mediated pathway (Brown et al., 2001).

Noteworthy are findings that in addition to cocaine and quinpirole, administration of the dopamine D2/3 agonist, pramipexole, increases vesicular dopamine uptake (Truong et al., 2003). These data seem paradoxical given that methamphetamine and methylenedioxymethamphetamine *decrease* vesicular dopamine uptake via a D2 receptor-mediated mechanism. Possible explanations for this discrepancy involve the distinct localization and function of D2 receptors, such as differential pre- and post-synaptic D2-associated mechanisms. This paradox underscores the complex actions regulating VMAT-2 function.

It was reported recently that a single injection of another dopamine reuptake inhibitor, methylphenidate, increases vesicular dopamine uptake and dihydrotetrabenazine binding in a vesicle-enriched subcellular fraction prepared from saline- or treated-rats. These increases occur rapidly (within 30 min) and reversibly. The increases in vesicular dopamine uptake do not result from residual methylphenidate introduced by the original in vivo treatment. In accord with these findings, a single injection of methylphenidate increases VMAT-2 immunoreactivity in the synaptic vesicle-enriched fractions prepared from treated rats. In addition, treatment with methylphenidate decreases VMAT-2 immunoreactivity in a plasmalemmal membrane-associated fraction, with no change in the whole synaptosomal fraction. Taken together, these data suggest that, like cocaine, methylphenidate redistributes VMAT-2 protein between the synaptosomal membrane and vesicle-enriched fractions (Sandoval et al., 2002).

Similar to effects of cocaine, eticlopride pretreatment antagonizes the increase in vesicular dopamine uptake, and prevents the methylphenidate-induced increases in dihydrotetrabenazine binding and VMAT-2 immunoreactivity in the vesicle-enriched fraction. Unlike the effects of cocaine, SCH23390 pretreatment attenuates the methylphenidate-induced increases in vesicular dopamine uptake, dihydrotetrabenazine binding and VMAT-2 immunoreactivity in the vesicle-enriched fraction. Coadministration of these antago-

nists inhibits completely the methylphenidate-related increase in vesicular dopamine sequestration and dihydrotetrabenazine binding in this fraction (Sandoval et al., 2002). The appearance of a D1 component in the methylphenidate-induced increase was unexpected, as cocaine presumably increases extracellular dopamine concentrations and hence would predictably have displayed a similar component: the lack of cocaine-induced dopamine D1 receptor-mediated VMAT-2 alterations may be due to factors such as the magnitude and/or duration of the cocaine-induced increase in extracellular dopamine concentrations.

The functional relevance of a methylphenidate-induced redistribution of VMAT-2 protein, and presumably associated vesicles, remains unknown. However, a predictable consequence would be altered dopamine disposition within nerve terminals. Accordingly, it was determined that methylphenidate increases vesicular dopamine content by greater than 200%, without altering homogenate dopamine concentrations (Sandoval et al., 2003). This finding is consistent with the hypothesis that methylphenidate redistributes vesicles from a membrane-associated to a vesicle-enriched subcellular fraction, thereby increasing the dopamine concentration in the latter compartment without affecting total striatal dopamine concentrations. These data suggest that the functional importance of the methylphenidate-induced vesicular trafficking involves a redistribution of intraneuronal dopamine.

As mentioned above, it has been hypothesized that high-dose methamphetamine treatment rapidly redistributes cytoplasmic dopamine within nerve terminals, leading to intraneuronal reactive oxygen species formation and well-characterized persistent dopamine deficits. As described above, in addition to this persistent damage, methamphetamine treatment rapidly decreases vesicular dopamine uptake; a phenomenon that may contribute to aberrant intraneuronal dopamine redistribution purportedly caused by the stimulant. Interestingly, *post-treatment* with dopamine transporter inhibitors attenuates the persistent dopamine deficits caused by methamphetamine (Marek et al., 1990; Sandoval et al., 2003); however, mechanisms underlying this phenomenon have not been elucidated. Recent studies by Sandoval et al. (2003) revealed that methylphenidate *post-treatment* both prevents the persistent dopamine deficits and reverses the acute decreases in vesicular dopamine uptake and dihydrotetrabenazine binding caused by methamphetamine treatment. In addition, methylphenidate post-treatment reverses the acute decreases in vesicular dopamine content caused by methamphetamine treatment. Taken together, these findings suggest that methylphenidate prevents persistent methamphetamine-induced dopamine deficits by redistributing vesicles and the associated VMAT-2 protein and presumably augmenting dopamine sequestration. Notably, a protective sequestering role for VMAT2 has been postulated. Among the suggestive data are findings that the toxic metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 1-methyl-4-phenylpyridinium, is sequestered within VMAT-2-containing neurons (Speciale et al., 1998). Of particular interest are findings by German et al. (2000) that striatal MPTP toxicity is enhanced if mice are treated with VMAT-2 inhibitors. Also of interest are findings that MPTP toxicity is enhanced in VMAT-2 heterozygote knockout mice (Takahashi et al., 1997). Thus, an understanding of the neuroprotective sequestering role of VMAT-2 and vesicles may not only provide insight into the neurotoxic effects of methamphetamine, but may also elucidate mechanisms underlying dopamine neurodegenerative disorders, including Parkinson's disease.

4. Other agents and VMAT-2

The majority of studies assessing psychostimulant-induced effects on VMAT-2 has involved dopamine reuptake inhibitors or releasers. However, other psychoactive agents have been demonstrated to rapidly impact VMAT-2. For example, lobeline is an alkaloidal constituent of *Lobelia inflata* classified as both an agonist and an antagonist at nicotinic receptors (for review, see Dwoskin and Crooks, 2002). It has been suggested that lobeline inhibits dopamine reuptake and thus redistributes dopamine within the presynaptic terminal via an interaction with the tetrabenazine-binding site on VMAT-2 (Teng et al., 1998).

In addition to lobeline, phencyclidine has been demonstrated to affect VMAT-2. Phencyclidine is a hallucinogen that is both an NMDA receptor antagonist and a dopamine reuptake inhibitor. In addition, it rapidly and reversibly increases vesicular dopamine uptake. In contrast, a similar pretreatment with another non-competitive NMDA receptor antagonist, dizocilpine ([5*R*,10*S*]-[+]-5-methyl-10,11-dihydro-5*H* dibenzo[*a*,*d*]cyclohepten-5,10-imine; MK-801), does not alter vesicular dopamine uptake suggesting that, as was the case with cocaine and methylphenidate, the dopamine reuptake blocking properties of this agent mediate the effects on VMAT-2. Consistent with this, pretreatment with eticlopride blocked the increase in vesicular dopamine uptake caused by phencyclidine suggesting that D2 receptors contribute to this phenomenon (Crosby et al., 2002).

5. Summary

As described above, psychostimulants differentially alter vesicular monoamine transporter function. There are also strong indications that these acute responses may contribute to, or at least be predictive of, their long-term neurochemical consequences. For instance, agents that tend to release dopamine through an action involving reversal of the plasmalemmal dopamine transporter such as methamphetamine appear to rapidly decrease vesicular monoamine transporter function in the cytosol, thus presumably increasing unsequestered cytoplasmic dopamine concentrations causing persistent dopaminergic neuronal damage. In contrast, agents that increase vesicular dopamine uptake in the vesicular-

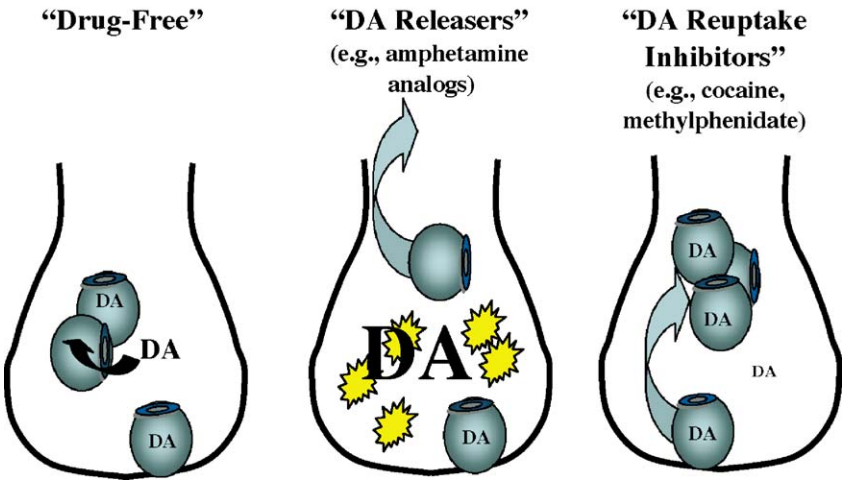

Fig. 1. Schematic representation of the effect of dopamine (DA) "releasers" and "reuptake inhibitors" on VMAT-2 distribution within nerve terminals. Under "drug-free" conditions, DA is sequestered within vesicles inside nerve terminals. In the presence of DA "releasers", VMAT-2 (and presumably vesicles) are redistributed such that the ability to sequester cytoplasmic DA has diminished. Hence, cytoplasmic DA accumulates and promotes formation of reactive oxygen species. In the presence of DA "reuptake inhibitors", VMAT-2 (and presumably vesicles) are redistributed to a non-membrane-associated, presumably cytoplasmic pool: consequently, sequestration of cytoplasmic DA is enhanced and cytoplasmic DA concentrations remain low.

enriched fraction such as cocaine or methylphenidate cause relatively little or no such deficits (Fig. 1). Of perhaps clinical relevance are findings that these plasmalemmal dopamine reuptake inhibitors can be neuroprotective against methamphetamine-induced neurodegeneration (Marek et al., 1990; Sandoval et al., 2003), perhaps by increasing dopamine sequestration within synaptic vesicles. Accordingly, these agents may be of benefit in treating neurodegenerative disorders such as Parkinson's disease wherein aberrantly high cytoplasmic dopamine concentrations may contribute to the loss of dopaminergic neurons. Future studies are necessary to investigate precise mechanisms whereby vesicle function, including trafficking, occurs. For example, recent studies demonstrate that alpha-synuclein, a protein aberrant in some Parkinson's disease families (Polymeropoulos et al., 1997), contributes to the regulation of synaptic vesicles within nerve terminals, at least in the hippocampus (Cabin et al., 2002). An understanding of how agents, including stimulants, alter the function of alpha-synuclein and similar proteins may have widespread implication for treatment of not only neurodegenerative disorders, but also an array of disease processes associated with aberrant monoaminergic transmission.

Acknowledgements

Several of the studies cited above were supported by DA00869, DA04222, DA 11389 and DA13367.

References

Anderson, B.B., Chen, G., Gutman, D.A., Ewing, A.G., 1998. Dopamine levels of two classes of vesicles are differentially depleted by amphetamine. Brain Res. 788, 294–301.

Brown, J.M., Hanson, G.R., Fleckenstein, A.E., 2000. Methamphetamine rapidly decreases vesicular dopamine uptake. J. Neurochem. 74, 2221–2223.

Brown, J.M., Hanson, G.R., Fleckenstein, A.E., 2001. Cocaine-induced increases in vesicular dopamine uptake: role of dopamine receptors. J. Pharmacol. Exp. Ther. 298, 1150–1153.

Brown, J.M., Riddle, E.L., Sandoval, V., Weston, R.K., Hanson, J.E., Crosby, M.J., Ugarte, Y.V., Gibb, J.W., Hanson, G.R., Fleckenstein, A.E., 2002. A single methamphetamine administration rapidly decreases vesicular dopamine uptake. J. Pharmacol. Exp. Ther. 302, 497–501.

Cabin, D.E., Shimazu, K., Murphy, D., Cole, N.B., Gottschalk, W., McIlwain, K.L., Orrison, B., Chen, A., Ellis, C.E., Palor, R., Lu, B., Nussbaum, R.L., 2002. Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha-synuclein. J. Neurosci. 22, 8797–8807.

Crosby, M.J., Hanson, J.E., Fleckenstein, A.E., Hanson, G.R., 2002. Phencyclidine increases vesicular dopamine uptake. Eur. J. Pharmacol. 438, 75–78.

Dwoskin, L.P., Crooks, P.A., 2002. A novel mechanism of action and potential use for lobeline as a treatment for psychostimulant abuse. Biochem. Pharmacol. 63, 89–98.

Erickson, J.D., Eiden, L.E., Hoffman, B.J., 1992. Expression cloning of a reserpine-sensitive vesicular monoamine transporter. Proc. Natl. Acad. Sci. U. S. A. 89, 10993–10997.

Fischer, J.F., Cho, A.K., 1979. Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model. J. Pharmacol. Exp. Ther. 208, 203–209.

Fleckenstein, A.E., Gibb, J.W., Hanson, G.R., 2000. Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. Eur. J. Pharmacol. 406, 1–13.

Frey, K.A., Koeppe, R.A., Kilbourn, M.R., Vander Borght, T.M., Albin, R.L., Gilman, S., Kuhl, D.E., 1996. Presynaptic monoaminergic vesicles in Parkinson's disease and normal aging. Ann. Neurol. 40, 873–884.

Fumagalli, F., Gainetdinov, R.R., Wang, Y.M., Valenzano, K.J., Miller, G.W., Caron, M.G., 1999. Increased methamphetamine neurotoxicity in heterozygous vesicular monoamine transporter 2 knock-out mice. J. Neurosci. 19, 2424–2431.

German, D.C., Liang, C.L., Manaye, K.F., Lane, K., Sonsalla, P.K., 2000. Pharmacological inactivation of the vesicular monoamine transporter

can enhance 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neurodegeneration of midbrain dopaminergic neurons, but not locus coeruleus noradrenergic neurons. Neuroscience 101, 1063–1069.

Gibb, J.W., Kogan, F.J., 1979. Influence of dopamine synthesis on methamphetamine-induced changes in striatal and adrenal tyrosine hydroxylase activity. Naunyn-Schmiedeberg's Arch. Pharmacol. 310, 185–187.

Gonzalez, A.M., Walther, D., Pazos, A., Uhl, G.R., 1994. Synaptic vesicular monoamine transporter expression: distribution and pharmacologic profile. Brain Res. Mol. Brain Res. 22, 219–226.

Graham, D.G., Tiffany, S.M., Bell Jr., W.R., Gutknecht, W.F., 1978. Autoxidation versus covalent binding of quinones as the mechanism of toxicity of dopamine, 6-hydroxydopamine, and related compounds toward C1300 neuroblastoma cells in vitro. Mol. Pharmacol. 14, 644–653.

Hansen, J.P., Riddle, E.L., Sandoval, V., Brown, J.M., Gibb, J.W., Hanson, G.R., Fleckenstein, A.E., 2002. Methylenedioxymethamphetamine decreases plasmalemmal and vesicular dopamine transport: mechanisms and implications for neurotoxicity. J. Pharmacol. Exp. Ther. 300, 1093–1100.

Harvey, D.C., Lacan, G., Melegan, W.P., 2000. Regional heterogeneity of dopaminergic deficits in vervet monkey striatum and substantia nigra after methamphetamine exposure. Exp. Brain Res. 133, 349–358.

Hastings, T.G., 1995. Enzymatic oxidation of dopamine: the role of prostaglandin H synthase. J. Neurochem. 64, 919–924.

Hogan, K.A., Staal, R.G., Sonsalla, P.K., 2000. Analysis of VMAT2 binding after methamphetamine or MPTP treatment: disparity between homogenates and vesicle preparations. J. Neurochem. 74, 2217–2220.

Hotchkiss, A., Gibb, J.W., 1980. Long-term effects of multiple doses of methamphetamine on tryptophan hydroxylase and tyrosine hydroxylase in rat brain. J. Pharmacol. Exp. Ther. 214, 257–262.

Hotchkiss, A., Morgan, M.E., Gibb, J.W., 1979. The long-term effects of multiple doses of methamphetamine on neostriatal tryptophan hydroxlase, tyrosine hydroxylase, choline acetyltransferase and glutamate decarboxylase activities. Life Sci. 25, 1373–1378.

Johnson, R.G., 1988. Accumulation of biological amines into chromaffin granules: a model for hormone and neurotransmitter transport. Physiol. Rev. 68, 232–307.

Johnson-Davis, K.L., Truong, J.G., Fleckenstein, A.E., Wilkins, D.G., 2003. The role of VMAT2 in the induction of tolerance to the neurotoxic effects of methamphetamine. Abstr.-Soc. Neurosci. Abstr. 962.8.

Jones, S.R., Gainetdinov, R.R., Wightman, R.M., Caron, M.G., 1998. Mechanisms of amphetamine action revealed in mice lacking the dopamine transporter. J. Neurosci. 18, 1979–1986.

Larsen, K.E., Fon, E.A., Hastings, T.G., Edwards, R.H., Sulzer, D., 2002. Methamphetamine-induced degeneration of dopaminergic neurons involves autophagy and upregulation of dopamine synthesis. J. Neurosci. 22, 8951–8960.

Lehericy, S., Brandel, J.P., Hirsch, E.C., Anglade, P., Villares, J., Scherman, D., Duyckaerts, C., Javoy-Agid, F., Agid, Y., 1994. Monoamine vesicular uptake sites in patients with Parkinson's disease and Alzheimer's disease, as measured by tritiated dihydrotetrabenazine autoradiography. Brain Res. 659, 1–9.

Liang, N.Y., Rutledge, C.O., 1982. Evidence for carrier-mediated efflux of dopamine from corpus striatum. Biochem. Pharmacol. 31, 2479–2484.

Little, K.Y., Krolewski, D.M., Zhang, L., Cassin, B.J., 2003. Loss of striatal vesicular monoamine transporter protein (VMAT2) in human cocaine users. Am. J. Psychiatry 160, 47–55.

Marek, G.J., Vosmer, G., Seiden, L.S., 1990. Dopamine uptake inhibitors block long-term neurotoxic effects of methamphetamine upon dopaminergic neurons. Brain Res. 513, 274–279.

Nirenberg, M.J., Liu, Y., Peter, D., Edwards, R.H., Pickel, V.M., 1995. The vesicular monoamine transporter 2 is present in small synaptic vesicles and preferentially localizes to large dense core vesicles in rat solitary tract nuclei. Proc. Natl. Acad. Sci. U. S. A. 92, 8773–8777.

Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I., Nussbaum, R.L., 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047.

Raiteri, M., Cerrito, F., Cervoni, A.M., Levi, G., 1979. Dopamine can be released by two mechanisms differentially affected by the dopamine transport inhibitor nomifensine. J. Pharmacol. Exp. Ther. 208, 195–202.

Ricaurte, G.A., Guillery, R.W., Seiden, L.S., Schuster, C.R., Moore, R.Y., 1982. Dopamine nerve terminal degeneration produced by high doses of methylamphetamine in the rat brain. Brain Res. 235, 93–103.

Riddle, E.L., Topham, M.K., Haycock, J.W., Hanson, G.R., Fleckenstein, A.E., 2002. Differential trafficking of the vesicular monoamine transporter-2 by methamphetamine and cocaine. Eur. J. Pharmacol. 449, 71–74.

Riddle, E.L., Hanson, G.R., Fleckenstein, A.E., in press. Amphetamine and methylphenidate differentially and selectively traffic the vesicular monoamine transporter-2. Abstr.-Soc. Neurosci.

Sandoval, V., Riddle, E.L., Hanson, G.R., Fleckenstein, A.E., 2002. Methylphenidate redistributes vesicular monoamine transporter-2: role of dopamine receptors. J. Neurosci. 22, 8705–8710.

Sandoval, V., Riddle, E.L., Hanson, G.R., Fleckenstein, A.E., 2003. Methylphenidate alters vesicular monoamine transport and prevents methamphetamine-induced dopaminergic deficits. J. Pharmacol. Exp. Ther. 304, 1181–1187.

Schmidt, C.J., Ritter, J.K., Sonsalla, P.K., Hanson, G.R., Gibb, J.W., 1985. Role of dopamine in the neurotoxic effects of methamphetamine. J. Pharmacol. Exp. Ther. 233, 539–544.

Schmitz, Y., Lee, C.J., Schmauss, C., Gonon, F., Sulzer, D., 2001. Amphetamine distorts stimulation-dependent dopamine overflow: effects of D2 autoreceptors, transporters, and synaptic vesicle stores. J. Neurosci. 21, 5916–5924.

Speciale, S.G., Liang, C.L., Sonsalla, P.K., Edwards, R.H., German, D.C., 1998. The neurotoxin 1-methyl-4-phenylpyridinium is sequestered within neurons that contain the vesicular monoamine transporter. Neuroscience 84, 1177–1185.

Staley, J.K., Talbot, J.Z., Ciliax, B.J., Miller, G.W., Levey, A.I., Kung, M.P., Kung, H.F., Mash, D.C., 1997. Radioligand binding and immunoautoradiographic evidence for a lack of toxicity to dopaminergic nerve terminals in human cocaine overdose victims. Brain Res. 747, 219–229.

Sulzer, D., Rayport, S., 1990. Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. Neuron 5, 797–808.

Sulzer, D., Maidment, N.T., Rayport, S., 1993. Amphetamine and other weak bases act to promote reverse transport of dopamine in ventral midbrain neurons. J. Neurochem. 60, 527–535.

Sulzer, D., Chen, T.K., Lau, Y.Y., Kristensen, H., Rayport, S., Ewing, A., 1995. Amphetamine redistributes dopamine from synaptic vesicles to the cytosol and promotes reverse transport. J. Neurosci. 15, 4102–4108.

Takahashi, N., Miner, L.L., Sora, I., Ujike, H., Revay, R.S., Kostic, V., Jackson-Lewis, V., Przedborski, S., Uhl, G.R., 1997. VMAT2 knockout mice: heterozygotes display reduced amphetamine-conditioned reward, enhanced amphetamine locomotion, and enhanced MPTP toxicity. Proc. Natl. Acad. Sci. U. S. A. 94, 9938–9943.

Teng, L., Crooks, P.A., Dwoskin, L.P., 1998. Lobeline displaces [3H]dihydrotetrabenazine binding and releases [3H]dopamine from rat striatal synaptic vesicles: comparison with D-amphetamine. J. Neurochem. 71, 258–265.

Thibaut, F., Faucheux, B.A., Marquez, J., Villares, J., Menard, J.F., Agid, Y., Hirsch, E.C., 1995. Regional distribution of monoamine vesicular uptake sites in the mesencephalon of control subjects and patients with Parkinson's disease: a postmortem study using tritiated tetrabenazine. Brain Res. 692, 233–243.

Truong, J.G., Horton, D.J., Hanson, G.R., Fleckenstein, A.E., 2003. Quinpirole increases vesicular dopamine uptake and redistributes vesicular monoamine transporter-2 protein. Abstr.-Soc. Neurosci. Abstr. 373.12.

Wagner, G.C., Ricaurte, G.W., Seiden, L.S., Schuster, C.R., Miller, R.J., Westley, J., 1980. Long-lasting depletions of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. Brain Res. 181, 151–160.

Wagner, G.C., Lucot, J.B., Schuster, C.R., Seiden, L.S., 1983. Alpha-methyltyrosine attenuates and reserpine increases methamphetamine-induced neuronal changes. Brain Res. 270, 285–288.

Wilson, J.M., Kalasinsky, K.S., Levey, A.I., Bergeron, C., Reiber, G., Anthony, R.M., Schmunk, G.A., Shannak, K., Haycock, J.W., Kish, S.J., 1996a. Striatal dopamine nerve terminal markers in human, chronic methamphetamine users. Nat. Med. 2, 699–703.

Wilson, J.M., Levey, A.I., Bergeron, C., Kalasinsky, K., Ang, L., Peretti, F., Adams, V.I., Smialek, J., Anderson, W.R., Shannak, K., Deck, J., Niznik, H.B., Kish, S.J., 1996b. Striatal dopamine, dopamine transporter, and vesicular monoamine transporter in chronic cocaine users. Ann. Neurol. 40, 428–439.

Woolverton, W.L., Ricaurte, G.A., Forno, L., Seiden, L.S., 1989. Long-term effects of chronic methamphetamine administration in rhesus monkeys. Brain Res. 486, 73–78.