New Insights into the Mechanism of Action of Amphetamines

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Key Words

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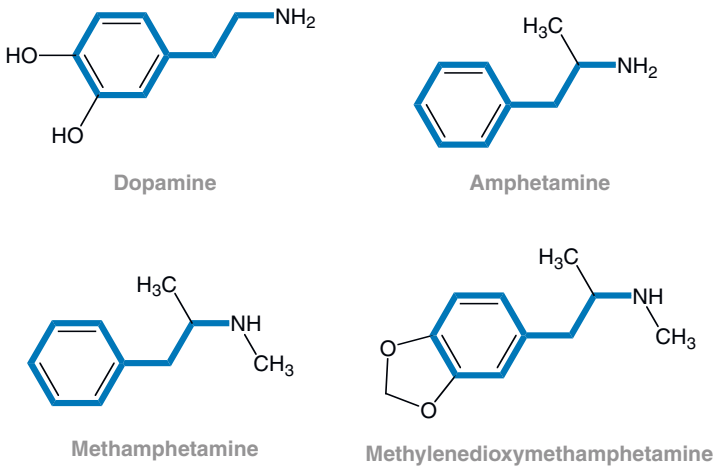
Abstract

Amphetamine is a psychostimulant commonly used to treat several disorders, including attention deficit, narcolepsy, and obesity. Plasmalemmal and vesicular monoamine transporters, such as the neuronal dopamine transporter and the vesicular monoamine transporter-2, are two of its principal targets. This review focuses on new insights, obtained from both in vivo and in vitro studies, into the molecular mechanisms whereby amphetamine, and the closely related compounds methamphetamine and methylenedioxymethamphetamine, cause monoamine, and particularly dopamine, release. These mechanisms include amphetamine-induced exchange diffusion, reverse transport, and channel-like transport phenomena as well as the weak base properties of amphetamine. Additionally, amphetamine analogs may affect monoamine transporters through phosphorylation, transporter trafficking, and the production of reactive oxygen and nitrogen species. All of these mechanisms have potential implications for both amphetamine- and methamphetamine-induced neurotoxicity, as well as dopaminergic neurodegenerative diseases.

Figure 1

Structural diagrams of dopamine and selected amphetamines. Features common to all structures are indicated in bold.



OVERVIEW

Amphetamine (1-methyl-2-phenethylamine, AMPH)* is a psychostimulant commonly used to treat several disorders, including attention deficit, narcolepsy, and obesity. It is one member of a collection of compounds referred to herein as amphetamines, many of which are comprised of a phenyl ring connected to an amino group by a two-carbon side chain with a methyl group on carbon-1 of the side chain (**Figure 1**). Methamphetamine (METH) and methylenedioxymethamphetamine (MDMA) are other members of this group. METH is widely abused for its ability to increase wakefulness and physical activity and decrease appetite. MDMA is an illicit stimulant/hallucinogen used, at least initially, to attain mental stimulation, emotional warmth, enhanced sensory perception, and increased physical energy. This review focuses on these agents, with a particular emphasis on recent studies providing new insights into their mechanism(s) of action.

AMPHETAMINES AND PLASMALEMMAL TRANSPORTERS

Introduction

Lazar Edeleano first synthesized AMPH in 1887, but it was not until 1910 that this and several of its analogs were tested in animal models [1; for an excellent review of the chemistry and metabolism of AMPH and its analogs, see Nichols (2) and Cho & Kumagai (3), respectively]. Years passed before Gordon Alles, in an effort

*Abbreviations used in text: Acute transporter response–dopamine-dependent (ATR_{DA}), acute transporter response–dopamine-independent (ATR_{IND}), acute transporter response (ATR), amphetamine (AMPH), dihydrotetrabenazine (DHTBZ), dopamine (DA), dopamine transporter (DAT), fluorescence resonance energy transfer (FRET), human dopamine transporter (hDAT), methamphetamine (METH), methylenedioxymethamphetamine (MDMA), methylphenidate (MPD), protein kinase A (PKA), protein kinase C (PKC), rat dopamine transporter (rDAT), serotonin or 5-hydroxytryptamine (5HT), vesicular monoamine transporter-2 (VMAT-2)

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to develop potent decongestants, independently synthesized the compound. He and his colleagues were among the first to report its stimulant effects (1; for an excellent review of the history of AMPH and its analogs, see also Reference 4).

Several more years passed before mechanisms underlying the action of AMPH began to be elucidated fully. By the late 1950s, researchers suggested that AMPH acts peripherally to release a "noradrenaline-like substance" (5). Years later, several studies demonstrated that AMPH released central catecholamines as well. Since then, numerous studies have focused on the impact of AMPH and its analogs on plasmalemmal transporters, including the dopamine (DA) transporter (DAT), serotonin (5-hydroxytryptamine, 5HT) transporter, and norepinephrine transporter, as reviewed below. Although AMPH and its analogs generally display comparable actions at the various transporters, the DAT is the protein most frequently implicated in their reinforcing properties and abuse potential. Thus, unless otherwise indicated, discussion of the impact of AMPH on plasmalemmal transporters will focus on the DAT. The reader is directed to several excellent recent reviews for additional discussion (4, 6–9).

Exchange Diffusion, Reverse Transport, and Channel-Like Transport

Several lines of evidence indicate that plasmalemmal transporters are the conduits through which AMPH causes monoamine release. Early evidence included findings by Raiteri et al. (10), who reported that AMPH releases DA by a mechanism that can be prevented by the DA reuptake inhibitor, nomifensine. Concurrently, Fischer & Cho (11) suggested an exchange diffusion model wherein extracellular AMPH substitutes or exchanges for DA and is transported into cells by the DAT. This increases the probability that cytosolic DA will bind to the DAT and be transported out down its concentration gradient. Thus, in this model, the DA-releasing effects of AMPH are caused by its ability to be transported by the DAT. Later, Liang & Rutledge (12) proposed a concentration-dependent dual mechanism of DA release. In particular, and when present at low concentrations, extracellular AMPH is exchanged for cytosolic DA via the DAT. However, at higher concentrations, AMPH, a highly lipophilic compound (13), diffuses into nerve terminals through the plasmalemmal membrane and liberates DA from intraneuronal binding sites allowing it to exit the terminal via DAT-mediated reverse transport.

For an exchange diffusion/reverse transport model to be correct, AMPH must be a substrate for DAT. The best evidence for AMPH as a transporter substrate came from Zaczek et al. (14), who demonstrated that AMPH accumulation was saturable, temperature-dependent, and ouabain-sensitive in striatal synaptosomes. These data also indicate active transport of the ligand. This accumulation was prevented by coincubation with the DAT reuptake inhibitors methylphenidate (MPD) and cocaine. Further important evidence that AMPH analogs are substrates for DAT came from electrophysiological studies involving *Xenopus* oocytes expressing the DAT (hDAT). Specifically, Sonders et al. (15) demonstrated that both METH and AMPH elicit DA-like transporter-associated currents. Likewise, Sitte et al. reported, "like the natural

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substrate DA, [AMPH is] transported and induces inward currents in DAT-expressing mammalian cells" (16).

Recent findings by Galli and coworkers (17) confirmed and extended the studies. Specifically, these researchers reported that AMPH causes DA efflux from neuronal cultures and heterologous cells stably expressing hDAT via two mechanisms. One involves a rapid, channel-like DAT configuration permitting millisecond bursts of DA. A second consists of a slower, exchange-like mechanism. Noteworthy, these authors estimate that while the channel-like mode is responsible for one tenth of AMPH-induced DA release, this release resembles vesicular release in both magnitude and timing and may therefore be involved in the psychostimulant effects of amphetamines (for discussion, see 17).

Still other evidence that AMPH is a substrate analog for the plasmalemmal DAT comes from findings that AMPH inhibits activity of the striatal DAT by competing with DA for a common binding site. Mazindol competitively inhibits striatal DAT at this substrate-binding site. This stands in contrast to cocaine that inhibits striatal DAT at a site separate from, but interacting with, that of substrate analogs (18). Thus, an overwhelming amount of data demonstrate that AMPH is a substrate for DAT, a feature predictably due to its similar chemical structure to DA (**Figure 1**).

Phosphorylation, Reactive Species Formation, and Internalization

In 1997, our laboratory (19) demonstrated that a single in vivo injection of the AMPH analog, METH, rapidly (within 1 h) and reversibly decreased plasmalemmal DA uptake, as assessed ex vivo in synaptosomes prepared from the striata of treated rats; an effect attributable to a decreased V_{max} of uptake. This effect was not due to residual METH that was introduced by its in vivo original administration. Furthermore, it was not associated with a decrease in binding of the DAT ligand, WIN 35428 (20). This decrease in uptake concurrent with a lack of effect on binding of this presumably membrane-permeable ligand was consistent with the possibility of DAT internalization; a phenomenon since characterized extensively in vitro (see discussion below). Transport of 5HT, but not norepinephrine, was affected similarly by METH treatment (21, 22). Noteworthy and similar to the ex vivo effect, incubation of striatal synaptosomes with METH rapidly decreased DAT activity, but not WIN 35428 binding. DAT phosphorylation likely contributed to this in vitro METH-induced deficit, as it was prevented by coincubation with a protein kinase C (PKC) inhibitor (23).

Phosphorylation. A role for PKC in the effects of AMPH analogs on DAT as assessed ex vivo was predictable, as AMPH application in vitro had been reported to increase striatal particulate PKC activity (24), and several investigators had reported downregulation of DAT function in vitro in response to PKC activation (25–31). The impact of PKC activation on DAT is, however, complex and involves not only uptake but release as well. In particular, application of a PKC activator can induce DA efflux (32, 33), and AMPH-induced DA efflux can be prevented by application of PKC inhibitors (32, 34). An association between DA release and DAT phosphorylation

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is further suggested by findings that mutation of the DAT N-terminus suppresses AMPH-induced DA efflux (35). Of relevance are findings that phosphorylation of the N-terminus of the DAT shifts it "from a reluctant state to a willing state for AMPH-induced DA efflux, without affecting inward transport" (35).

Adding to the complexity are findings of Giambalvo (36) that AMPH and DA may have dual effects on PKC activity. During efflux of exogenous DA, PKC activity is stimulated. Conversely, the inward transport of AMPH inhibits PKC activity. The stimulatory effect of AMPH application in vitro requires both intracellular calcium and endogenous DA (24, 36). In a subsequent study, she reported that phospholipases C and A(2) are involved in the AMPH-induced changes in PKC activity (24).

Elegant studies by Vaughan and coworkers (37) directly addressed whether treatment with AMPH analogs in vivo altered DAT phosphorylation. In particular, they found that a single administration of METH to rats increased DAT phosphorylation. This was demonstrated ex vivo in rats sacrificed 30 min after treatment by measuring $^{32}PO_4$ labeling of striatal DAT. METH application in vitro to rat DAT (rDAT) LLC-PK(1) cells or striatal tissue also increased $^{32}PO_4$ metabolic labeling. Both the METH-induced phosphorylation and a concurrent downregulation of DA transport in vitro were prevented by coapplication of a PKC inhibitor, a transport finding similar to that reported previously (23). Importantly, METH-induced phosphorylation of DAT was not observed in an N-terminally truncated protein lacking the first 21 residues, including six serines (i.e., a site of phosphorylation by phorbol esters), while the decrease in DAT activity was still present. Taken together, these data suggest METH can alter DAT function via phosphorylation-dependent and phosphorylation-independent mechanisms (37).

Reactive Species Formation. One mechanism whereby METH can decrease DAT function, presumably independent of transporter phosphorylation, involves reactive species formation. Exposure to either reactive oxygen or nitrogen species can alter DAT function (e.g., 38–40). Further, METH exposure can promote formation of these reactive species (for review, see 41–44). Among the first demonstrations of this was work by Cubells et al. (45), who applied METH to postnatal ventral midbrain DA neuron cultures and provided data suggesting that METH treatment rapidly alters vesicular DA sequestration that can, in turn, promote aberrant accumulation of intraneuronal DA and subsequently reactive species formation. The interplay between the vesicular monoamine transporter-2 (VMAT-2, a protein primarily responsible for vesicular DA sequestration) and DAT function is discussed further below.

Internalization. Among the reasons that AMPH analog-induced DAT phosphorylation has received considerable attention is speculation that it may contribute to internalization of the transporter. Several studies in vitro have implicated that phosphorylation is key to internalization. For example, in 1997, Zhu et al. (46) reported that application of a PKC activator decreased DA uptake in oocytes expressing the cloned hDAT and decreased the binding of the DAT ligand, mazindol, in intact oocytes. This treatment did not alter total binding of mazindol, suggesting that phosphorylation contributes to internalization of the DAT. Similarly, Pristupa et al. (31)

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utilized confocal microscopy to demonstrate that PKC activation rapidly internalized the hDAT from the plasmalemmal membrane, whereas PKC/PKA inhibition led to recruitment of these transporters to the cell surface. Subsequent and important studies confirmed and extended findings that PKC activation can decrease surface DAT expression in vitro (47). This decrease in surface expression appears to be due to an increase in DAT endocytosis coupled with a reduction in recycling back to the plasmalemmal membrane (48). Importantly, not all internalization is entirely PKC-mediated, as distinct mechanisms underlying constitutive transporter internalization have been described (49).

In 2000, Galli and coworkers (50) utilized both confocal microscopy and electophysiological techniques to demonstrate that application of AMPH caused DAT internalization, as assessed in HEK-293 cells stably expressing the hDAT. The loss of cell surface DAT was observed using confocal microscopy as early as 20 min after AMPH treatment and was maximal after 1 h, a time frame consistent with the decrease in DAT activity observed 1 h after METH treatment by our laboratory (see above) that presumably reflected, at least in part, DAT internalization. Sorkina et al. (51) extended these findings by demonstrating in vitro that AMPH application induced an intracellular hDAT accumulation in endosomes. Using fluorescence resonance energy transfer technology (FRET) involving stably transfected cells, these investigators provided evidence that once internalized, the DAT formed oligomers. The formation of oligomers in vivo after AMPH analog treatment is discussed below.

Although considerable attention has focused on internalization and effects beginning at least several minutes after treatment, Gnegy and coworkers (52) utilized biotinylation of rat striatal synaptosomes to label surface DAT and thereby study DAT redistribution at very early time points. These investigators found that AMPH application rapidly (within 30 s), but briefly (lasting less than 2.5 min), increased synaptosomal DAT surface expression, an increase prevented by cocaine pretreatment and associated with increased delivery of DAT to the plasmalemmal membrane. DA application per se did not mimic this effect. AMPH application did not alter DA uptake, but it did increase basal and AMPH-induced DA efflux.

Additional Complexities

The in vivo studies mentioned above describe the impact of a single administration of an AMPH analog. Particularly, a single METH injection causes a rapid and reversible decrease in DAT function that is not associated with a change in B_{max} of binding of WIN 35428 (19, 20, 53). In contrast, many studies have focused on the acute impact of repeated administrations of the stimulant. Regimens such as these involving 3–5 injections administered at 2–6-h intervals were originally designed to mimic the "runs" wherein abusers binged on these agents. Like the effect of a single METH injection, multiple METH administrations rapidly decreased DAT function as well, as assessed in rat striatal synaptosomes prepared 1 h after the final METH treatment, an effect attributable to a reduced V_{max} and an unchanged $K_{m.}$ (20). However, the magnitude of the effect was greater than that resulting from a single injection, allowing for the possibility that the decrease resulting from repeated injections is comprised of

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more than one phenomenon. Noteworthy, a similar decrease has also been observed in mice (54). This METH-induced decrease is not due to residual drug introduced by the original subcutaneous injections nor to an acute loss of DAT protein (20). In contrast to the effects of a single METH injection, it is associated with a decrease in WIN 35428 binding. Also, in contrast with effects of a single METH treatment, this effect is only partially reversed 24 h later (20).

A series of studies comparing mechanisms underlying the acute effects of single and repeated METH administrations have provided insight into the differential regulation of the DAT. DA per se contributes to at least one component of the rapid decrease in DAT activity caused by repeated METH injections, as pretreatment with alpha-methyl-*p*-tyrosine (a tyrosine hydroxylase inhibitor that causes DA depletion), a D1 antagonist (SCH23390), or a D2 antagonist (eticlopride) partially attenuated this deficit. In contrast, these treatments did not alter the response of DAT to a single METH injection. Furthermore, prevention of METH-induced hyperthermia attenuated the deficit caused by repeated stimulant treatments, but did not alter the effect of a single METH administration. Finally, pretreatment with the radical scavenger, N-t-butyl-alpha-phenylnitrone, partially inhibited the decrease caused by multiple, but not a single, METH treatment (55). From these studies, it has been suggested that the response to repeated METH injections is comprised of at least two distinct phenomena. The first is a rapidly reversing acute transporter response (ATR) that resembles the effects of a single METH injection (i.e., is temperature- and DA-independent, is not associated with a change in B_{max}, and recovers during the first 24 h after treatment; ATR_{IND}). The second is a DA-, temperature-, and reactive species–sensitive acute transporter response (ATR_{DA}) that persists for at least 24 h after drug treatment and is associated with a decrease in WIN 35428 binding (for review, see 56). Whether these ATRs occur independently or if the ATR_{IND} is permissive for the ATR_{DA} remains to be elucidated.

In addition to the decrease in uptake described above, Baucum et al. (57) reported that multiple administrations of METH promoted formation of higher molecular weight (>170 kDa) DAT-associated protein complexes, as assessed in synaptosomal preparations 24–48 h after treatment. These findings were remarkable in that these data are among the first to demonstrate complex formation in vivo. Prior to this finding, radiation inactivation studies suggested that the DAT can exist as an oligomer (58). Cysteine crosslinking studies further indicated the possibility of symmetrical dimers (59), whereas mutational analysis indicated that a critical motif in the second transmembrane domain region of the DAT is important for DAT oligomerization (60). Further and as noted above, FRET studies have suggested that once internalized, DATs form oligomers (51).

As with deficits in DA uptake, both prevention of hyperthermia and pretreatment with alpha-methyl-*p*-tyrosine attenuated METH-induced DAT complex formation (57). In contrast, a single injection of METH or multiple injections of MDMA (i.e., treatments that, unlike METH, cause little or no persistent DA deficits) caused minimal complex formation (57). Sulfhydryl bridges likely contribute to complex formation because coincubation with the reducing agent, beta-mercaptoethanol, converts some complexes from a greater than 170 kDa to a 70 kDa species. Whether the DAT

is binding to itself, other large proteins, or a combination of these possibilities has yet to be determined.

AMPH AND VESICULAR MONOAMINE TRANSPORTERS

It has long been recognized that in addition to the DAT, the VMAT-2 is a critical mediator of AMPH-induced DA release (for review, see (4)). A recent study involving purified striatal vesicles demonstrated that METH-induced DA efflux has an initial velocity of 0.54 ± 0.08 fmol/s/μg protein and is blocked by application of the VMAT-2 inhibitor, tetrabenazine (61). Another study has shown that adolescent rats have less METH-induced vesicular DA efflux than young adult rats, which may contribute to their resistance to the effects of METH (62). Mechanisms whereby AMPH and its analogs alter vesicular DA sequestration are described below.

The Weak Base Hypothesis

It is widely accepted that the weak base properties of AMPH and its analogs contribute to its ability to disrupt vesicular storage within nerve terminals. AMPH is a lipophilic weak base with a pK_a of 9.9 (64). As it is presumed that like chromaffin granules, the interior of catecholaminergic vesicles is acidic [i.e., the pH of chromaffin granules is approximately 5.5 (4, 63)], intravesicular AMPH would accept protons once sequestered within this environment. It is predicted that this alkalinizes vesicles: a phenomenon suggested by findings involving cultured midbrain neurons and in isolated chromaffin granules (64). According to this weak base hypothesis, AMPH enters the cell through transport and lipophilic diffusion and then diffuses through the vesicular membrane and accumulates in vesicles. This disrupts the proton electrochemical gradient required for vesicular DA sequestration and causes increased cytoplasmic DA accumulation. The elevated cytoplasmic DA concentrations and altered concentration gradient reverse transport of DA via the plasmalemmal DAT (64, 65). In this model, elevated cytosolic DA levels and disruption of vesicular sequestration cause DA release via the DAT, independent of the actions of AMPH on the DAT. Unlike the plasmalemmal transporter exchange diffusion model described above, this model does not require a mobile site that mediates transport across the membrane, a suggestion supported by findings that weak bases that cause AMPH-like release, but are not substrates for DAT, induce reverse transport in DA cell cultures (65, 66).

Noteworthy, and in addition to its weak base properties, AMPH binds the VMAT-2 with relatively low (micromolar) affinity (67). Thus, by preventing vesicular DA uptake, AMPH may increase cytoplasmic DA concentrations and also promote plasmalemmal DA exchange.

Although widely accepted, a few observations have yet to be explained by the weak base hypothesis. Among these are findings by Floor & Meng (68) that AMPH (3 μM) depleted greater than 50% of radiolabeled DA from isolated synaptic vesicles, while only causing a 12% decrease in the proton gradient. A far better correlation was observed when high concentrations (i.e., greater than 100 μM) of AMPH were applied, although the physiological relevance of these concentrations is unclear.

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Redistribution of VMAT-2

In addition to disrupting the proton gradient and thereby DA sequestration, accumulating evidence indicates yet another effect of AMPH analogs on VMAT-2 function. In particular, Brown et al. (69) first demonstrated that repeated, high-dose administrations of METH to rats rapidly (within 1 h) decreased vesicular DA uptake, as assessed in vesicles purified from striata of treated rats. This largely involved dopaminergic nerve terminals because destruction of the striatal serotonergic projections did not alter vesicular DA transport in this preparation. Concurrently, Sonsalla and coworkers (70) reported that METH treatment decreased both DA uptake and binding of the VMAT-2 ligand, dihydrotetrabenazine (DHTBZ), as assessed in mice 24 h after treatment in a purified vesicular preparation. However and importantly, no significant loss of DHTBZ binding was observed in whole striatal homogenates at this time point. These data were the first to highlight the "disparity between homogenates and vesicle preparations" (70), and they provided an important clue suggesting the possibility that VMAT-2 was redistributed within nerve terminals after METH treatment.

Consistent with a redistribution hypothesis, Riddle et al. (71) reported that repeated, high-dose METH administrations rapidly (within 1 h) redistribute rat striatal VMAT-2 immunoreactivity from synaptic vesicle-enriched, nonmembrane (presumably cytoplasmic) subcellular fractions to a location not retained in the preparation of the synaptosomes. This decrease occurs concurrent with a METH-induced decrease in vesicular DA content in the enriched vesicular fraction (72). Subsequently, Yamamoto and coworkers (73) also demonstrated that METH decreased VMAT-2 immunoreactivity 1 and 24 h after treatment in a similar preparation.

The decrease in vesicular DA uptake caused by METH appears common among agents that cause DA release. For instance, a single injection of AMPH rapidly decreased vesicular DA uptake in a similar fashion (E.L. Riddle, unpublished observation). Repeated administration of MDMA likewise decreases striatal vesicular dopamine transport, but unlike effects of multiple repeated METH injections, the MDMA-induced decrease partially recovers by 24 h after drug treatment (74).

The effects of DA-releasing agents, such as AMPH and its analogs, are distinctly different than effects of reuptake inhibitors, such as cocaine and methylphenidate (MPD) (75–76). Administration of these agents to rats rapidly (within 1 h) increases both DA uptake and DHTBZ binding, as assessed ex vivo in a vesicle-enriched, nonmembrane-associated fraction. A similar phenomenon is observed in mice (77). The cocaine- and MPD-induced increases in uptake correspond to a shift in VMAT-2 protein from a plasmalemmal membrane-associated to a vesicle-enriched, nonmembrane-associated fraction (71, 76).

D2 receptors contribute to the AMPH analog-induced alteration in VMAT-2 function. Evidence for this includes findings that the decreases in vesicular DA uptake caused by a single METH or multiple MDMA injections are attenuated by pretreatment with the D2 antagonist, eticlopride (74, 78). The role of D2 receptors in affecting vesicular DA uptake and VMAT-2 redistribution is complex, as D2 antagonist pretreatment also attenuates cocaine- and MPD-induced increases in

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vesicular DA uptake and/or VMAT-2 distribution into nonmembrane-associated (presumably cytoplasmic) subcellular fractions (75, 76). Similar to the effects of reuptake inhibitors, treatment with the dopamine D2 agonists increases vesicular DA uptake, DHTBZ binding, and VMAT-2 immunoreactivity (75, 79–81). This paradox underscores the complexity of mechanisms regulating VMAT-2 function.

DAT and VMAT-2: Co-Contributors to DA Release?

While a role for DAT in AMPH-induced DA release has long been recognized, the relative contribution of alterations in vesicular sequestration to this phenomenon has been less clear. This is a consequence of disparate findings involving pretreatment with the VMAT-2 inhibitor, reserpine. Consonent with a role for vesicular DA as contributing to AMPH-induced DA release, some studies have demonstrated that reserpine treatment attenuates this phenomenon (82, 83). Other studies have found relatively little or no effect of the pretreatment (84–86). Interpretation of these studies may have been confounded by findings that reserpine can inhibit plasmalemmal DA uptake (87).

Using mice lacking the DAT, Jones et al. (88) reported that both depletion of DA from vesicles and reversal of DAT are necessary for DA release. Vesicular DA depletion is the rate-limiting step in this process. Moreover, the plasmalemmal DAT is not necessary for vesicular DA depletion by AMPH. Finally, increases in intracellular DA per se may not be sufficient to reverse the transport unless AMPH is present, as evidenced by findings that application of a VMAT-2 inhibitor did not increase wild-type striatal slice DA overflow unless AMPH was also applied to the preparation.

One important study indicating a role for both a plasmalemmal and a vesicular component to the DA-releasing action of AMPH was conducted by Pifl and colleagues (89) and involved COS-7 cells transfected with either the cDNA of the DAT, VMAT, or both. Application of AMPH rapidly increased DA release in cells expressing the DAT or expressing both the DAT and VMAT. Upon prolonged AMPH exposure, DA efflux from the DAT-transfected cells returned to baseline, whereas in cells containing both the DAT and VMAT, DA efflux was sustained.

AMPHETAMINES, TRANSPORTERS, AND NEUROTOXICITY

Repeated high-dose administrations of the AMPH analog, METH, cause persistent dopaminergic deficits (i.e., reductions in striatal DA content, DAT density, and/or activity of the DA synthesizing enzyme tyrosine hydroxylase) in rodents (90, 91), nonhuman primates (92), and/or humans (93–94). We and others have hypothesized that DA per se contributes to this persistent deficit. In particular and as described above, METH disrupts vesicular DA storage and induces a redistribution of VMAT-2 protein, resulting in aberrant cytosolic DA accumulation. This, in turn, promotes formation of DA-associated reactive oxygen species, thereby contributing to persistent deficits. The DAT and VMAT-2 likely contribute to this phenomenon because these

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proteins are principal regulators of DA distribution and storage. Accordingly, the role of these transporters in effecting METH-induced deficits has received considerable attention (for reviews, see 41, 56, 95).

Data indicating a role for the DAT in the deficits caused by METH include findings that administration of DAT inhibitors attenuates the DA deficits caused by METH treatment (96, 97). Schmidt & Gibb (96) were among the first to suggest that the ability of the DAT uptake inhibitor, amfonelic acid, to prevent the METH-induced deficits was due to an inhibition of transporter-mediated DA efflux rather than transporter-mediated uptake of METH. Furthermore, DAT knockout mice are resistant to the persistent deficits caused by the stimulant (98).

The VMAT-2 also contributes to the persistent DA deficits caused by METH, as evidenced by findings that reserpine pretreatment worsens this damage (99). Moreover, VMAT-2 heterozygote knockout mice are more susceptible to METH-induced DA deficits than wild-type controls (100). In addition, METH treatment of ventral midbrain neuronal cultures prepared from VMAT-2-deficient mice caused greater degeneration of DA neurites and accumulation of DA-associated reactive species compared with control cultures (101). Finally, important evidence suggesting that aberrant VMAT-2 function contributes to the persistent DA deficits caused by METH includes findings that posttreatment with the pharmacologically distinct agents MPD (72) and lobeline (73) reverse METH-induced alterations in VMAT-2 as assessed 6 and 24 h after METH exposure, respectively. These treatments also rescue DA neurons (i.e., prevent persistent DA deficits). Thus, given that the neurochemical deficits induced by the METH model are, at least in part, deficits associated with dopaminergic neurodegenerative disorders, study of the role of transporters as contributing to this damage merits attention.

CONCLUSION

Considerable effort has been devoted toward understanding mechanisms whereby AMPH and its analogs affect monoaminergic neuronal function. In vivo and in vitro studies, such as those described above, have not only elucidated the mechanisms of AMPH and its analogs on monoaminergic systems, but also provide critical understanding of the physiological and pathological processes associated with monoaminergic function and regulation. This insight can lay the foundation for comprehending the basis of not only drug abuse and addiction and the cellular nature of neurodegenerative events but also may suggest leads for developing related novel and more effective therapeutic strategies.

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