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Interaction of the anorectic medication, phendimetrazine, and its metabolites with monoamine transporters in rat brain

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Abstract

Phendimetrazine is an effective and widely prescribed appetite suppressant. Preclinical findings show that phendimetrazine displays stimulant properties similar to amphetamine, but few studies have examined the neurochemical mechanism of the drug. In the present work, we characterize the activity of phendimetrazine and its putative metabolites [phenmetrazine, pseudophenmetrazine, and associated stereoisomers] at biogenic amine transporters. All drugs were tested in vitro using assays to measure uptake and release of [^{3}H]dopamine, [^{3}H]norepinephrine, and [^{3}H]serotonin ([^{3}H]5-HT) in rat brain synaptosomes. Selected drugs were tested in vivo using microdialysis to measure extracellular dopamine and serotonin (5-HT) in rat nucleus accumbens. Phendimetrazine itself had no effect on uptake or release of any transmitter. In contrast, the *trans*-configured *N*-demethylated metabolite, phenmetrazine, was a potent releaser of [^{3}H]norepinephrine (EC_{50} = 50 nM) and [^{3}H]dopamine (EC_{50} = 131 nM). The *cis* *N*-demethylated metabolite, pseudophenmetrazine, displayed modest potency at releasing [^{3}H]norepinephrine (EC_{50} = 514 nM) and blocking [^{3}H]dopamine re-uptake (IC_{50} = 2630 nM). All drugs tested were inactive or weak in the [^{3}H]5-HT assays. When injected intravenously, phendimetrazine had minimal effects on extracellular transmitter levels, whereas phenmetrazine produced dose-related elevations in extracellular dopamine. The collective findings suggest that phendimetrazine is a "prodrug" that is converted to the active metabolite phenmetrazine, a potent substrate for norepinephrine and dopamine transporters. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Phendimetrazine; Phenmetrazine; Dopamine; Norepinephrine; Microdialysis

1. Introduction

Phendimetrazine (Fig. 1, structure **1**) is a clinically available medication that displays biochemical and behavioral properties similar to amphetamine (Corwin et al., 1987; De La Garza and Johanson, 1987; Evans and Johanson, 1987; Foltin, 1989; Jones and Holtzman, 1994). Phendimetrazine is approved for short-term use in the treatment of obesity (Bray, 1993; Ryan, 2001). Additionally, due to its weak stimulant properties, phendimetrazine might prove useful as an agonist substitution pharmacotherapy for stimulant addictions (Baumann and Rothman, 1998; Grabowski et al., 2001; Rothman et al., 1998a). Following oral administration of phendimetrazine to human subjects, 30% of the drug dosage is recovered in urine as the ***N***-demethylated metabolite, phenmetrazine (Fig. 1, structure **2**) (Beckett and Raisi, 1976). The extent to which phenmetrazine contributes to the actions of systemically administered phendimetrazine is not known. Moreover, little information exists on the precise neurochemical actions of phendimetrazine or phenmetrazine.

Preclinical studies indicate that the behavioral effects of phendimetrazine can be influenced by route of drug administration. When administered by the intraperitoneal (i.p.) route to rats, phendimetrazine increases locomotor activity but is much less potent than amphetamine (Jones and Holtzman, 1994). Drug discrimination studies in monkeys indicate that orally administered (p.o.) phendimetrazine and phenmetrazine are about equipotent in their ability to generalize to the amphetamine stimulus cue (De La Garza and Johanson, 1987). Interestingly, intravenous (i.v.) phendimetrazine does not support self-administration behavior in monkeys whereas i.v. phenmetrazine is readily self-admin-

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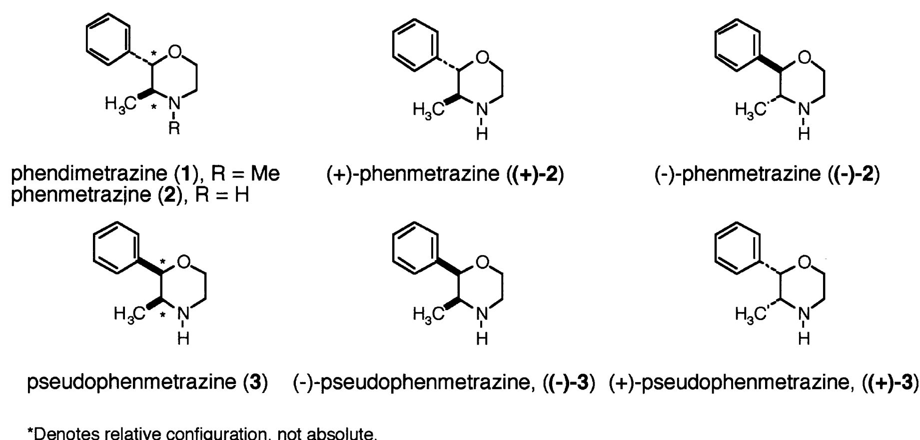

Fig. 1. Structures of phendimetrazine, phenmetrazine, and its stereoisomers.

istered (Corwin et al., 1987). Taken together, the available data suggest phendimetrazine might be a "prodrug" that is metabolized after systemic administration to generate phenmetrazine, the pharmacologically active entity.

The clinically available form of phendimetrazine is a racemic mixture. Both phendimetrazine and phenmetrazine contain two chiral centers, with their corresponding methyl and phenyl substituents oriented in a *trans* configuration relative to the morpholine ring (Fig. 1, structures **1** and **2**). Pseudophenmetrazine (Fig. 1, structure **3**) contains the same two chiral centers, but the methyl and phenyl substituents are oriented in a ***cis*** configuration. Since little information exists on the neurochemical actions of phendimetrazine or its putative metabolites, we sought to determine the activity of these compounds at biogenic amine transporters. All drugs were tested in vitro using assays to measure uptake and release of $[^3H]$dopamine, $[^3H]$norepinephrine, and $[^3H]$5-HT in rat brain synaptosomes. Selected compounds were tested in vivo using microdialysis to measure extracellular dopamine and 5-HT in rat nucleus accumbens.

2. Methods

2.1. Animals

Male Sprague–Dawley rats (300–400 g) were obtained from Charles River Laboratories (Wilmington, MA). The animal housing facilities were fully accredited by the American Association of the Accreditation of Laboratory Animal Care (AAALAC), and all experiments were performed within the guidelines delineated in the Institutional Care and Use Committee of the National Institute on Drug Abuse (NIDA), Intramural Research Program.

2.2. Transporter-related assays

The assays used to determine the ability of test drugs to influence the re-uptake and release of $[^3H]$dopamine, $[^3H]$norepinephrine, and $[^3H]$5-HT were performed according to published methods (Rothman et al., 2000). Briefly, crude synaptosomes were prepared from rat caudate (for dopamine re-uptake and release assays) or from whole brain minus caudate (for norepinephrine and 5-HT re-uptake and release assays) by homogenizing freshly excised tissue in ice-cold 10% sucrose using 12 strokes of a Potter–Elvehjem homogenizer. Homogenates were centrifuged at $1000 \times g$ for 10 min. Supernatants were retained on ice and used immediately in re-uptake and release assays.

All assays were performed in Krebs–phosphate buffer (pH 7.4) that contained 154.4 mM NaCl, 2.9 mM KCl, 1.1 mM $CaCl_2$, 0.83 mM $MgCl_2$, 5 mM glucose, 1 mg/ml ascorbic acid, and 50 μM pargyline. For the release assays, 1 μM reserpine was added to the sucrose solution and assay buffer. $[^3H]$Norepinephrine re-uptake and release assays were performed in the presence of 5 nM 3β-(4-Iodophenyl)-tropane-2β-pyrrolidine carboxamide tartrate (RTI-229) to prevent re-uptake of $[^3H]$norepinephrine into dopaminergic nerves. $[^3H]$5-HT re-uptake and release assays were performed in the presence of 100 nM nomifensine and 100 nM GBR12935 to prevent re-uptake of $[^3H]$5-HT into noradrenergic and dopaminergic nerves. Incubation times were 15, 10, and 30 min for $[^3H]$dopamine, $[^3H]$norepinephrine, and $[^3H]$5-HT re-uptake, respectively.

For release assays, synaptosomal preparations were incubated to steady state with 5 nM $[^3H]$dopamine (30 min), 7 nM $[^3H]$norepinephrine (60 min), or 5 nM $[^3H]$5-HT (60 min). Synaptosomes preloaded with neurotransmitter were added to test tubes containing test drugs and incubated for 5 min ($[^3H]$dopamine and $[^3H]$5-HT) or 30 min ($[^3H]$norepinephrine). At the designated time, assays were filtered using a Packard Filtermate Harvester. Non-displaceable tritium was measured by conducting incubations in the presence of 10 μM tyramine for $[^3H]$dopamine and $[^3H]$norepinephrine release and 100 μM tyramine for $[^3H]$5-HT release. The filters were dried for 1 h at 60 °C and counted using the Packard Topcount-NXT™ Microplate Scintillation and Luminescence Counter.

Table 1
Comparison of neurotransmitter re-uptake inhibition and release by phendimetrazine and phenmetrazine stereoisomers

	Dopamine		Norepinephrine		Serotonin	
	Re-uptake $IC_{50} \pm$ S.D. (nM)	Release $EC_{50} \pm$ S.D. (nM)	Re-uptake $IC_{50} \pm$ S.D. (nM)	Release $EC_{50} \pm$ S.D. (nM)	Re-uptake $IC_{50} \pm$ S.D. (nM)	Release $EC_{50} \pm$ S.D. (nM)
Phendimetrazine, **1**	19,000 ± 537	>10,000	8300 ± 445	>10,000	>100,000	>100,000
Phenmetrazine, **2**	607 ± 51	131 ± 11	153 ± 19	50.4 ± 5.4	>10,000	7765 ± 610
(+)-Phenmetrazine, **(+)-2**	359 ± 23	87.4 ± 7.8	240 ± 24	37.5 ± 4.3	>10,000	3246 ± 263
(−)-Phenmetrazine, **(−)-2**	1669 ± 189	415 ± 45	388 ± 54	62.9 ± 9.5	>10,000	>10,000
Pseudophenmetrazine, **3**	2630 ± 198	Uptake blocker	453 ± 39	514 ± 52	>10,000	>10,000
(−)-Pseudophenmetrazine, **(−)-3**	2691 ± 176	Uptake blocker	2512 ± 321	2511 ± 561	>10,000	>10,000
(+)-Pseudophenmetrazine, **(+)-3**	3320 ± 195	1457 ± 138	270 ± 27	349 ± 28	>10,000	>10,000

[^{3}H]dopamine, [^{3}H]5-HT, and [^{3}H]norepinephrine re-uptake and release assays were conducted as described in Methods. Values are means of three experiments ± S.D.

2.3. In vivo microdialysis

Surgical implantation of indwelling jugular catheters and intra-accumbens guide cannulae was carried out as previously described (Baumann et al., 1994). On the evening prior to testing, extension tubes were connected to catheters, and microdialysis probes (2 × 0.5 mm exchange surface, CMA/12, CMA/Microdialysis) were inserted into the nucleus accumbens via the guide cannulae. Dialysis probes were perfused in situ overnight with artificial cerebrospinal fluid (aCSF) containing 150 mM NaCl, 3 mM KCl, 1.4 mM $CaCl_2$, and 0.8 mM $MgCl_2$, pumped at a flow rate of 1.0 μl/min. The next morning dialysate samples were collected at 20-min intervals. Samples were immediately assayed for endogenous dopamine and 5-HT using high-pressure liquid chromatography, as described elsewhere (Baumann et al., 2000). Three baseline samples were collected and subsequent dopamine and 5-HT measures were expressed as a percent of this baseline. Probe recoveries of dopamine and 5-HT ranged from 18% to 20%. Drug solutions were prepared immediately before use and doses are expressed as the salt.

2.4. Data analysis, chemicals, and reagents

Determination of IC_{50} values (for inhibition of re-uptake) and EC_{50} values (for stimulation of release) were carried out using the nonlinear least-squares curve-fitting program MLAB-PC (Civilized Software, Bethesda, MD), as previously described. In the release assays, "specific" displaceable tritium was calculated as the difference between total retained tritium and non-displaceable tritium. In some instances, test drugs increased non-displaceable tritium; when this occurred, the non-displaceable tritium was measured for each test drug concentration. K_i values were calculated from IC_{50} or EC_{50} values using published methods (Rothman et al., 1998b). In some release experiments, the apparent K_i of transporter blocking agents was deter-

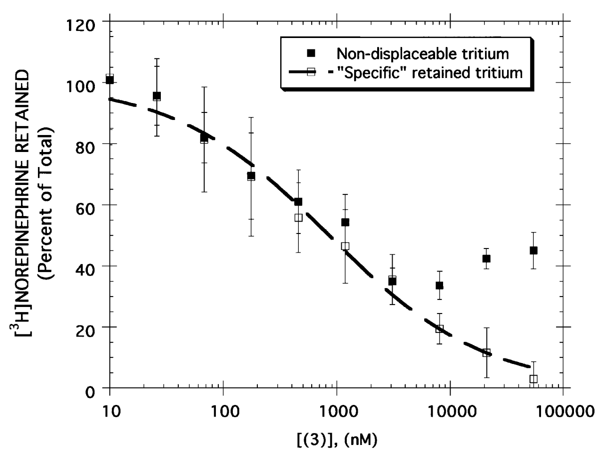

Fig. 2. Effect of pseudophenmetrazine (**3**) on [^{3}H] norepinephrine release. Pseudophenmetrazine (**3**) dose–response curves in the [^{3}H] norepinephrine release assay were generated as described in Methods in the absence and presence of 10 μM tyramine. "Specific" displaceable tritium was calculated as: total retained tritium minus non-displaceable tritium. Each value is the mean ± S.D. ($n = 3$).

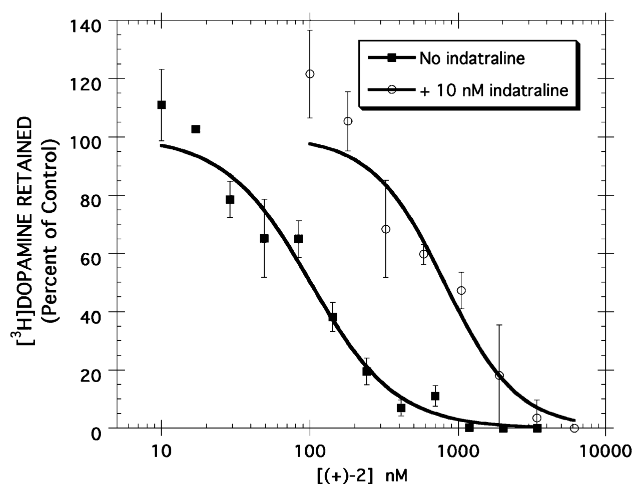

Fig. 3. Evidence that (+)-phenmetrazine (**(+)-2**) is a substrate of the dopamine transporter. **(+)-2** dose–response curves in the [^{3}H]dopamine release assay were generated in the absence (EC_{50} = 99 nM) and presence of 10 nM indatraline (EC_{50} = 810 nM). Each value is the mean ± S.D. ($n = 3$).

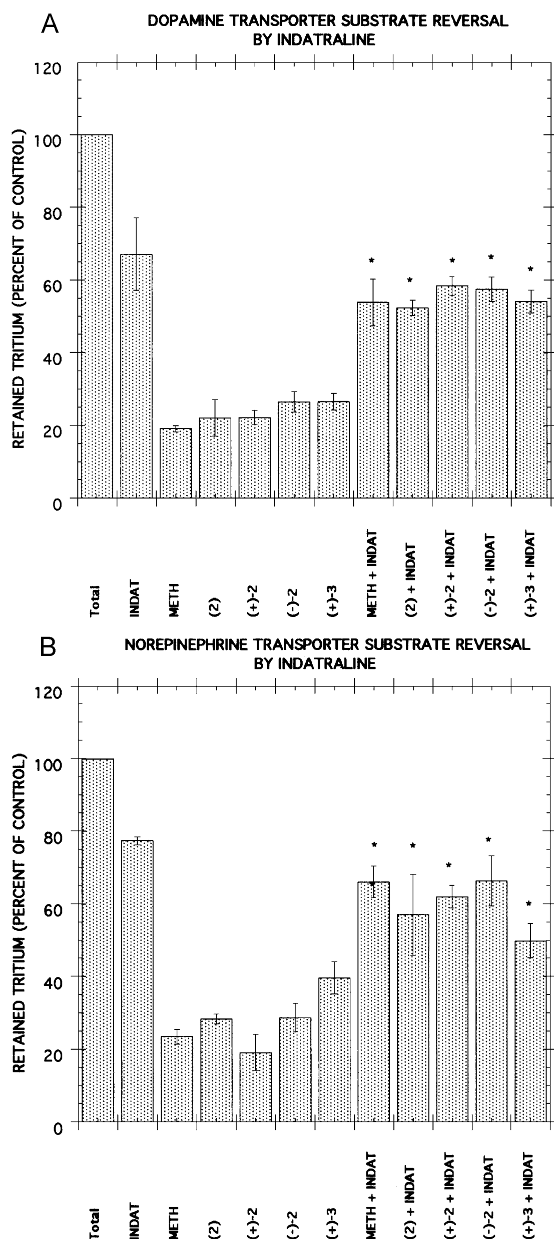

Fig. 4. Substrate activity of **2**, **(+)-2**, **(−)-2**, and **(+)-3** in the [^{3}H]norepinephrine and [^{3}H]dopamine release assays. Approximately ED_{80} concentrations of the test compound was tested in the absence and presence of 10 nM indatraline for activity in the [^{3}H]dopamine (panel A) and [^{3}H]norepinephrine (panel B) release assays. Each value is the mean ± S.D. ($n = 3$). $*p < 0.05$ when compared to the drugs alone (Student's *t*-test). Panel A: the drug concentrations were: indatraline (INDAT, 20 nM), (+)-methamphetamine (METH, 20 nM), **2** (500 nM), **(+)-2** (250 nM), **(−)-2** (1500 nM), **(+)-3** (5000 nM). Panel B: indatraline 200 nM, METH, 75 nM, **2** (250 nM), **(+)-2** (200 nM), **(−)-2** (250 nM), **(+)-3** (2000 nM).

mined by measuring the EC_{50} value of a releasing drug in the absence ($EC_{50\text{-}1}$) and presence ($EC_{50\text{-}2}$) of the blocker agent (Rothman et al., 2000). The K_i was calculated according to the following equation: K_i=[Blocking agent]/($EC_{50\text{-}2}$/$EC_{50\text{-}1} - 1$). For the microdialysis experiments, the first three samples collected before any treatment were considered baseline and all subsequent monoamine measures were expressed as a percent of this baseline. Data were evaluated by one-way analysis of variance with repeated measures. Sources of reagents and chemicals are published (Rothman et al., 2001). The synthesis of phenmetrazine and its stereoisomers will be described (manuscript in preparation).

3. Results

3.1. In vitro experiments

Racemic phendimetrazine (**1**) was essentially inactive at [^{3}H]dopamine, [^{3}H]norepinephrine, and [^{3}H]5-HT uptake inhibition and release (Table 1). The most potent effect of **1** was inhibition of [^{3}H]norepinephrine uptake, with an IC_{50} of 8300 nM. Racemic phenmetrazine (**2**), and both of its stereoisomers (**(+)-** and **(−)-2**), released [^{3}H]dopamine more potently than they inhibited [^{3}H]dopamine uptake. Their releasing ability displayed stereoselectivity, since **(+)-2** was more potent at [^{3}H]dopamine release ($EC_{50} = 87$ nM) than **(−)-2** ($EC_{50} = 415$ nM). Phenmetrazine released [^{3}H]norepinephrine more potently than it inhibited [^{3}H]norepinephrine uptake, and this effect was also stereoselective. As noted with other substrate-type stimulants (Rothman et al., 2000, 2001), **2** and its stereoisomers were more potent at stimulating [^{3}H]norepinephrine release than [^{3}H]dopamine release. For example, **(−)-2** was 6.6-fold more potent in the [^{3}H]norepinephrine release assay ($EC_{50} = 62.9$ nM) than in the [^{3}H]dopamine release assay ($EC_{50} = 415$ nM). **2** released [^{3}H]5-HT with an EC_{50} value of 7800 nM, indicating that these compounds are about 100-fold more potent at releasing norepinephrine than releasing 5-HT.

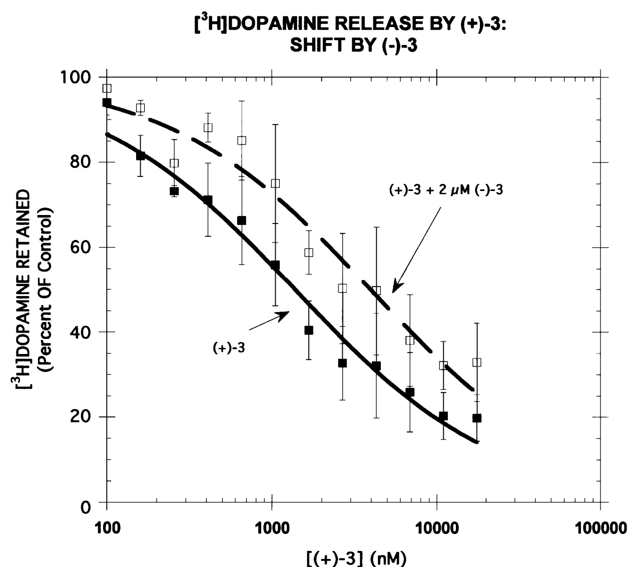

Fig. 5. Dopamine transporter substrate activity of (+)-pseudophenmetrazine (**(+)-3**). **(+)-3** dose–response curves in the [^{3}H]dopamine release assay were generated in the absence ($EC_{50} = 1384$ nM) and presence of 2 μM **(−)-3** ($EC_{50} = 3976$ nM). Each value is the mean ± S.D. ($n = 3$).

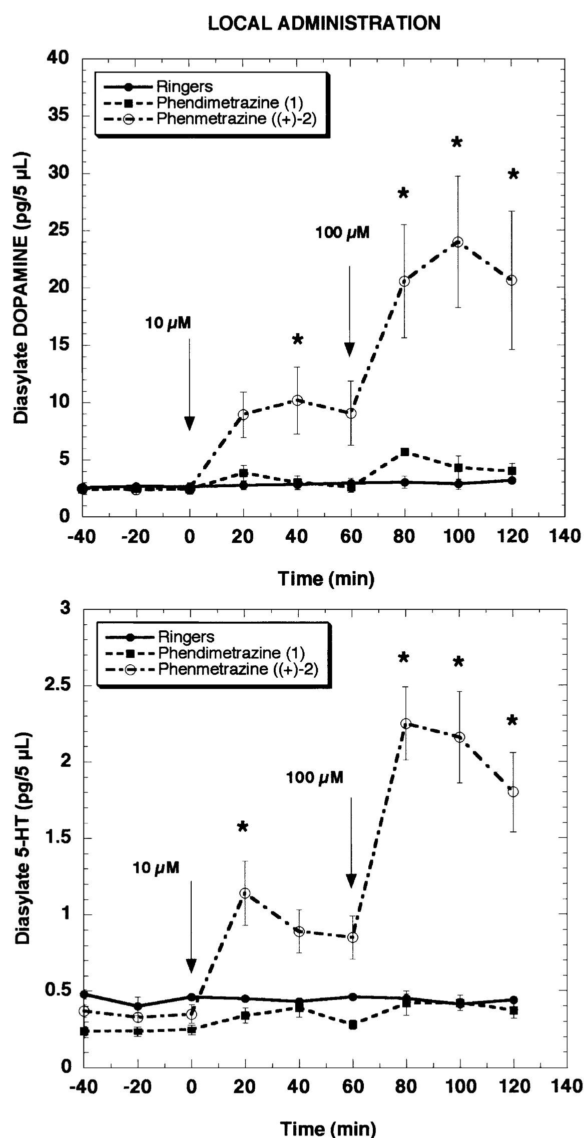

Fig. 6. Effect of locally administered phendimetrazine (**1**) and (+)-phenmetrazine **(+)-2** on extracellular dopamine (top panel) and 5-HT (bottom panel) in rat n. accumbens. Each value is the mean ± SEM ($n = 6-7$ rats).

Racemic pseudophenmetrazine (**3**), and both of its stereoisomers (**(+)−** and **(−)-3**), were at least 10-fold weaker at releasing [^{3}H]norepinephrine when compared to the phenmetrazine analogs. The norepinephrine-releasing activity of **(+)-3** ($EC_{50} = 349$ nM) was 10-fold more potent than **(−)-3** ($EC_{50} = 2511$ nM). Whereas **3** and **(−)-3** were weak [^{3}H]dopamine uptake inhibitors (IC_{50} values of about 2.7 μM), **(+)-3** was a weak [^{3}H]dopamine releaser. **3** and its stereoisomers were essentially inactive in releasing [^{3}H]5-HT. Interestingly, **3** increased the non-displaceable retained tritium. This is illustrated in Fig. 2 for [^{3}H]norepinephrine release. As described, the non-displaceable tritium was measured for each test drug concentration.

Dose–response shift experiments were conducted to verify the substrate activity of selected compounds. As reported in Fig. 3, 10 nM indatraline, which by itself had minimal activity in the [^{3}H]dopamine release assay, shifted the **(+)-2** dose–response curve to the right. Based on the degree of shift, the apparent K_i of indatraline for the dopamine transporter was calculated to be 1.4 nM, which is similar to what we reported previously (Rothman et al., 2000). To verify the substrate activity of **2**, **(+)-2**, **(−)-2** and **(+)-3**, approximately ED_{80} concentrations were tested in the [^{3}H]norepinephrine and [^{3}H]dopamine release assays in the absence and presence of 10 nM indatraline. As reported in Fig. 4, indatraline reversed the releasing activity of all these agents, indicating that they are transporter substrates.

It is of interest that the stereoisomers **(−)-3** and **(+)-3** interact at the dopamine transporter as uptake inhibitor and

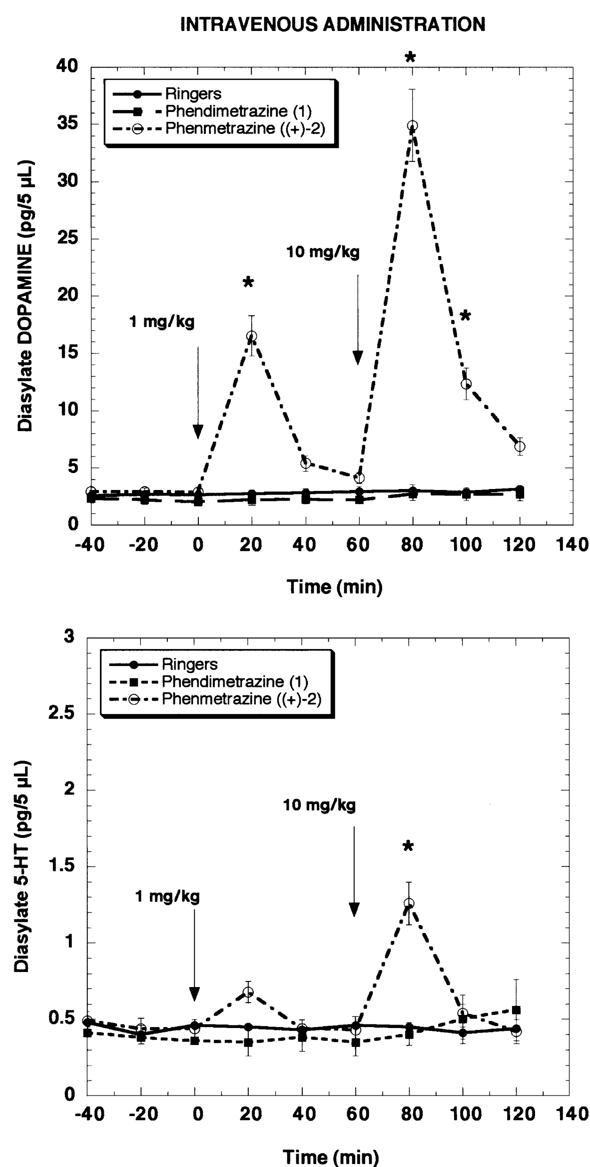

Fig. 7. Effect of phendimetrazine (**1**) and (+)-phenmetrazine **(+)-2** administered i.v. on extracellular dopamine (upper panel) and 5-HT (lower panel) in rat n. accumbens. * $p < 0.01$ when compared to saline. Each value is the mean ± SEM ($n = 6-7$ rats).

substrate, respectively. To further verify these findings, we determined the ability of **(−)-3** to shift the **(+)-3** dose–response curve to the right. As reported in Fig. 5, 2 μM **(−)-3**, which by itself had minimal effects in the [^{3}H]dopamine release assay, shifted the **(+)-3** dose–response curve to the right. Based on the degree of shift, the apparent K_i of **(−)-3** for the dopamine transporter was calculated to be 1025 nM, which is similar to its reported K_i for inhibiting [^{3}H]dopamine uptake (2691 nM, Table 1). The ability of **(−)-3** to block the [^{3}H]dopamine releasing effect of **(+)-3** may explain why the racemic mixture tests as a dopamine uptake inhibitor.

3.2. In vivo microdialysis experiments

We determined the ability of **1** and **(+)-2** to increase extracellular dopamine and 5-HT via local infusion of the drugs into the n. accumbens since this route of administration avoids metabolism. As reported in Fig. 6, **1** failed to increase extracellular dopamine or 5-HT levels. In contrast, **(+)-2** increased extracellular dopamine, and extracellular 5-HT to a lesser extent, in a dose-dependent manner. As reported in Fig. 7, when administered i.v., **1** failed to increase extracellular dopamine or 5-HT, whereas **(+)-2** significantly increased extracellular dopamine at both the 1 mg/kg ($F(2,12) = 44.42$, $p < 0.0001$) and 3 mg/kg ($F(2,12) = 78.54$, $p < 0.0001$) doses. **(+)-2** significantly increased extracellular 5-HT only at the 3 mg/kg dose ($F(2,12) = 10.02$, $p < 0.01$).

4. Discussion

The purpose of the current study was to clarify the neurochemical mechanism of action of the clinically available appetite suppressant, phendimetrazine. It has been established that orally administered phendimetrazine is metabolized to phenmetrazine in human subjects (Beckett and Raisi, 1976), but the role of the metabolite in mediating pharmacological effects of systemically administered phendimetrazine is not known. Studies in monkeys show that i.v. phendimetrazine does not support self-administration behavior, whereas the metabolite phenmetrazine is readily self-administered. (Corwin et al., 1987). These observations, coupled with the behavioral data mentioned in Introduction, led us to hypothesize that phendimetrazine is a prodrug that produces its stimulant effects via generation of the active metabolite, phenmetrazine. The data reported here fully support the prodrug hypothesis.

When tested in vitro, phendimetrazine was essentially inactive at dopamine, norepinephrine, and 5-HT transporters. By contrast, the *N*-demethylated metabolite phenmetrazine was a potent substrate-type releaser at dopamine transporters ($EC_{50} = 131$ nM) and norepinephrine transporters ($EC_{50} = 50$ nM). When administered locally into the n. accumbens via reverse dialysis so as to avoid metabolism, (+)-phendimetrazine failed to elevate extracellular dopamine or 5-HT. Locally applied (+)-phenmetrazine, on the other hand, increased extracellular dopamine in a dose-dependent manner. Finally, i.v. phendimetrazine failed to elevate extracellular dopamine or 5-HT, whereas equivalent doses of (+)-phenmetrazine produced a large and dose-dependent increase in extracellular dopamine.

Interestingly, local administration of (+)-phenmetrazine into the n. accumbens elevated extracellular 5-HT, despite the fact that the drug has more than 30-fold greater potency at releasing dopamine than 5-HT (Table 1). This apparent discrepancy might arise because local drug administration creates a concentration gradient, where neurons closer to the probe are exposed to higher drug concentrations than neurons further away from the probe. Upon systemic drug administration, in contrast, all neurons in the area around the probe are exposed to the same drug concentration. In the present local administration experiments, we speculate that neurons in the area immediately surrounding the probe are exposed to high enough concentrations of (+)-phenmetrazine to stimulate release of 5-HT. As the concentration of (+)-phenmetrazine in the perfusate is increased, more neurons in a "cylinder of influence" are exposed to the threshold concentration of the drug and the level of 5-HT in the dialysate increases. Consistent with this notion, i.v. administration of (+)-phenmetrazine increased extracellular 5-HT a modest 3-fold (Fig. 7) at the highest dose tested (3 mg/kg). We plan studies to determine the effect of phendimetrazine and (+)-phenmetrazine on extracellular norepinephrine.

As a clinically available central nervous system (CNS) stimulant, phendimetrazine represents a potential agonist substitution pharmacotherapy for cocaine addiction. Theoretically, stimulant-type appetite suppressants like phendimetrazine might normalize cocaine-dysregulated neurochemistry and thereby facilitate abstinence (Baumann and Rothman, 1998; Grabowski et al., 2001; Rothman et al., 1998a). Our data indicate that phendimetrazine generates two active compounds, (+) and (−) stereoisomers, which release dopamine and norepinephrine. Since peripheral administration of phenmetrazine elevates extracellular levels of 5-HT only at very high doses, therapeutic doses of the drug would not be expected to normalize the 5-HT deficit seen in cocaine withdrawal states (Baumann and Rothman, 1998). Thus, phendimetrazine and its metabolites may not be the medicines of choice for treating cocaine dependence.

The stereoisomers of phenmetrazine are about five to seven times more potent at releasing norepinephrine than dopamine, suggesting the predominant effect of phendimetrazine is to release norepinephrine. This observation provides further evidence that norepinephrine may play an important role in mediating stimulant-induced subjective effects in humans (Rothman et al., 2001). In this regard, it would be of interest to determine, in humans, the effect of phendimetrazine on dopamine-mediated pharmacological effects such as suppression of plasma prolactin secretion

and displacement of radiolabeled raclopride-binding using positron emission tomography (Villemagne et al., 1999).

Stereochemistry was found to have a striking affect on transporter activity. The *trans*-configured stereoisomers (i.e., phenmetrazines) were potent dopamine and norepinephrine releasers, whereas the *cis* stereoisomers (i.e., pseudophemetrazines) were weaker in this regard. A more interesting finding was that pseudophenmetrazine stereoisomers differed in their precise mode of interaction with dopamine transporters. Specifically, (−)-pseudophenmetrazine was a dopamine uptake inhibitor while (+)-pseudophenmetrazine was a dopamine releaser. To our knowledge, this is the first example of stereoisomers that exhibit this type of differential activity at the dopamine transporters.

Viewed collectively, these results strongly suggest that phendimetrazine is a prodrug, generating the active metabolite, phenmetrazine. Phenmetrazine is a substrate for the norepinephrine and dopamine transporters. The low potency of phenmetrazine for releasing 5-HT in comparison to releasing norepinephrine suggests that phendimetrazine (or phenmetrazine) would not be expected to normalize cocaine-induced neurochemical dysregulation, but could be useful for treating attention deficit disorder. Methylphenidate, the most common treatment for attention deficit disorder, is a potent inhibitor of norepinephrine and dopamine uptake (Biederman and Spencer, 1999). In regards to its use as an anorectic agent, our data suggest that therapeutic doses of phendimetrazine would release both dopamine and norepinephrine, unlike phentermine, which would be expected to selectively release norepinephrine (Rothman et al., 2001). Thus, our data suggest that phendimetrazine and phentermine may produce different neurochemical effects at therapeutic doses in humans.

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