The AAPS Journal 2006; 8 (1) Article 24 (http://www.aapsj.org).

Themed Issue: Drug Addiction - From Basic Research to Therapies
Guest Editors - Rao Rapaka and Wolfgang Sadée

Development of the Dopamine Transporter Selective RTI-336 as a Pharmacotherapy for Cocaine Abuse

Submitted: October 25, 2005; Accepted: December 23, 2005; Published: March 24, 2006

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ABSTRACT

The discovery and preclinical development of selective dopamine reuptake inhibitors as potential pharmacotherapies for treating cocaine addiction are presented. The studies are based on the hypothesis that a dopamine reuptake inhibitor is expected to partially substitute for cocaine, thus decreasing cocaine self-administration and minimizing the craving for cocaine. This type of indirect agonist therapy has been highly effective for treating smoking addiction (nicotine replacement therapy) and heroin addiction (methadone). To be an effective pharmacotherapy for cocaine addiction, the potential drug must be safe, long-acting, and have minimal abuse potential. We have developed several 3-phenyltropane analogs that are potent dopamine uptake inhibitors, and some are selective for the dopamine transporter relative to the serotonin and norepinephrine transporters. In animal studies, these compounds substitute for cocaine, reduce the intake of cocaine in rats and rhesus monkeys trained to self-administer cocaine, and have demonstrated a slow onset and long duration of action and lack of sensitization. The 3-phenyltropane analogs were also tested in a rhesus monkey self-administration model to define their abuse potential relative to cocaine. Based on these studies, 3β-(4-chlorophenyl)-2β-[3-(4'-methylphenyl)isoxazol-5-yl]tropane (RTI-336) has been selected for preclinical development.

KEYWORDS: RTI-336, dopamine transporter, cocaine abuse, pharmacotherapy, 3-aryltropanes

INTRODUCTION

Drug abuse, addiction, and dependence represent a major and increasing threat to public health. Cocaine abuse has been an epidemic in the United States since the introduction of crack in the mid-1980s. The 2003 National Survey on Drug Use and Health (NSDUH) estimated that 34.9 million Americans, aged 12 and older, have used cocaine at least once in their lifetime, that 5.9 million used cocaine in the past year, and that 2.3 million Americans are current users—some frequently, others occasionally (NSDUH report).[1] In 2002, the estimated number of cocaine-related emergency episodes totaled over 199 000.[2] While these numbers on use and cost show the magnitude of the drug abuse problem, the human suffering is incalculable. Illness, crime, domestic violence, reduced productivity, and lost opportunity are direct consequences of drug abuse. There is an increasing understanding that drug abuse is a physiologic disorder and that the need for medications for the treatment of drug abuse is tremendous. Even though several pharmacological agents have been tried on the basis of various hypotheses, none of the pharmacotherapeutic approaches has proven effective.[3-6] To address this critical deficiency, National Institute on Drug Abuse (NIDA) has made the development of an anticocaine medication a high priority.

In vitro studies have demonstrated that cocaine blocks the presynaptic uptake of dopamine, serotonin, and norepinephrine. However, it is the dopamine transporter (DAT) that is believed to be the critical recognition site for cocaine, mediating the behavioral and reinforcing effects that contribute to its abuse liability.[7-11] Numerous cocaine-discrimination and self-administration studies in laboratory animals support this conclusion.

A dopamine reuptake inhibitor would be expected to partially substitute for cocaine, thus decreasing cocaine self-administration and minimizing the craving for cocaine. This type of substitution pharmacotherapy has been highly effective for treatment of nicotine addiction (nicotine gum and patch) and heroin addiction (methadone). The development of a comparable drug for cocaine addiction would allow control of the behavior of the abuser until a strategy for long-term abstinence could be developed. We have discovered novel 3-phenyltropane analogs that are dopamine-selective reuptake inhibitors. It is hoped that one of these compounds will be useful as a medication for treating cocaine addicts without deleterious side effects.[12]

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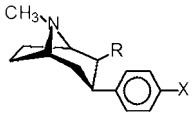
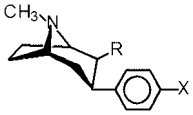
Table 1. 3β-Phenyltropane 2-Ester Analogs Selective for the DAT



Compound RTI-4229-	X	R	IC$_{50}$, nM (K$_i$, nM) DA [^{3}H]WIN 35,428	NE [^{3}H]Nisoxetine	5-HT [^{3}H]Paroxetine	NE/DA[a] Ratio	5-HT/DA* Ratio
Cocaine	—	—	89.1	3298 (1987)	1045 (95)	37	12
WIN 35,065-2	H	CO_2CH_3	23	920 (554)	2000 (182)	40	87
190	Cl	$CO_2C_3H_5$	0.96	235 (142)	168 (15.3)	245	175
114	Cl	$CO_2CH(CH_3)_2$	1.40	778 (469)	1400 (122)	555	1000
193	CH_3	$CO_2C_3H_5$	1.68	644 (388)	1070 (92)	383	637
113	Cl	$CO_2C_6H_5$	1.98	2960 (1783)	2340 (212)	1490	1180
436	$C_6H_5CH{=}CH$	CO_2CH_3	3.09	1960 (1181)	335 (31)	634	108
120	CH_3	$CO_2C_6H_5$	3.26	5830 (3512)	24,500 (2227)	1788	7515
150	CH_3	$CO_2C_4H_7$	3.74	4740 (2855)	2020 (134)	1267	540
204	Cl	$CO_2C_6H_4CH_3(2')$	3.91	4780 (2880)	3770 (342)	1223	964
277	NO_2	$CO_2C_6H_5$	5.94	5700 (3434)	2910 (265)	960	490
430	$C_6H_5(CH_2)_2C{\equiv}C$-	CO_2CH_3	6.28	1470 (886)	2182 (198)	234	348
117	CH_3	$CO_2CH(CH_3)_2$	6.45	1930 (1153)	6090 (554)	299	944
278	NO_2	$CO_2CH(CH_3)_2$	8.14	4100 (2170)	2150 (196)	504	264
205	CH_3	$CO_2C_6H_4CH_3(3')$	8.19	2130 (1283)	5240 (427)	260	640
203	Cl	$CO_2C_6H_4CH_3(3')$	9.37	2740 (1651)	2150 (196)	292	230
145	Cl	$CH_2OCO_2CH_3$	9.6	1480 (892)	2930 (266)	154	305

*Ratios of IC$_{50}$ values.

Table 2. 3β-Phenyltropane 2β-Amide Analogs Selective for the DAT



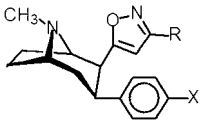
Compound RTI-4229-	X	R	IC$_{50}$, nM (K$_i$, nM) DA [^{3}H]WIN 35,428	NE [^{3}H]Nisoxetine	5-HT [^{3}H]Paroxetine	NE/DA* Ratio	5-HT/DA* Ratio
Cocaine	—	—	89.1	3298 (1906)	1045 (95)	37	12
WIN 35,065–2	H	CO_2CH_3	23	920 (555.6)	2000 (182)	40	87
227	I	$CONOCH_2CH_2CH_2$	0.75	357 (275)	129 (11.7)	476	172
218	Cl	$CONCH_3(OCH_3)$	1.19	8563 (5158)	1910 (174)	7200	1605
129	Cl	$CON(CH_3)_2$	1.38	942 (568)	1079 (98.1)	683	781
147	Cl	$CON(CH_2)_4$	1.38	3950 (2375)	12,400 (1120)	2862	8985
208	Cl	$CONOCH_2CH_2CH_2$	1.47	1080 (650)	2470 (225)	735	1680
186	CH_3	$CONCH_3(OCH_3)$	2.55	442 (266)	3400 (309)	173	1333
214	Cl	$CONCH_2CH_2OCH_2CH_2$	2.90	8550 (5750)	88,800 (8070)	2948	30,620
217	Cl	$CONHC_6H_4OH(2')$	4.78	31,000 (7867)	16,800 (1530)	6485	3515
215	Cl	$CON(C_2H_5)_2$	5.48	5530	9430 (857)	1009	1720
156	Cl	$CON(CH_2)_5$	6.95	1750 (1054)	3470 (315)	252	499

*Ratios of IC$_{50}$ values.

Over the last several years, we synthesized several 3-phenyltropane analogs and evaluated them for binding at the dopamine, serotonin, and norepinephrine transporters (DAT, 5-HTT, and NET, respectively). Forty-seven compounds showed selectivity for the DAT relative to the 5-HTT and NET, based on their relative IC_{50} values.[12,13] The binding affinities of these compounds are compared with cocaine and 3-phenyltropane 2-carboxylic acid methyl ester (WIN 35,065-2) in Tables 1-4. The compounds possess either a 4-chloro or 4-methylphenyl group at the 3β-position of the tropane ring and have an ester, amide, isoxazole, oxadiazole, benzthiazole, benzimidazole, or thiazole group in the 2β-position. The 15 RTI compounds shown in Table 1 have various ester groups in the 2β position of the tropane ring. The affinity for the dopamine transporter varies from 0.96 nM for RTI-190 to 9.6 nM for RTI-145. The affinities for the ten 2β amides listed in Table 2 vary from 0.75 nM for RTI-227 to 6.95 nM for RTI-156. Note the very high DAT selectivity for RTI-147, RTI-214, and RTI-218. The affinities for the 2β-isoxazoles listed in Table 3 vary from 0.50 nM for RTI-334 to 8.7 nM for RTI-371. Table 4 compares the inhibition of radioligand binding at the dopamine, norepinephrine, and serotonin transporters to those of cocaine and WIN 35,065-2 for 6 different other 2β heterocyclic analogs. Together, these compounds possess sufficient structural diversity to provide considerable variation in physicochemical properties. Furthermore, given their close structural similarity to other RTI compounds with known behavioral activity (RTI-32, -55, -113, -121, and -130),[14,15] it was expected that these compounds would both cross the blood-brain barrier and possess behavioral activity.

In designing a potential pharmacotherapy for cocaine abuse, other pharmacological activities must also be considered. Evidence from both animal and human studies suggests that the pharmacokinetic and pharmacodynamic properties of cocaine are important in reinforcement.[16-22] It is well known that cocaine gets into the brain quickly after peripheral administration and produces a "high" in 1 to 4 minutes.[16-18] This relatively rapid onset of action apparently contributes to cocaine's high efficacy as a reinforcer. Therefore, to minimize the possibilities of abuse, an ideal indirect agonist clinical candidate for cocaine addiction would have a slow onset of action. Samaha and Robinson[23] have demonstrated

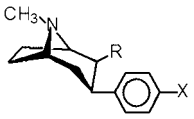
Table 3. 3β-Phenyltropane 2β-Isoxazole Analogs Selective for the DAT

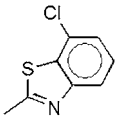
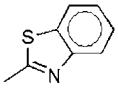
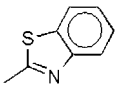
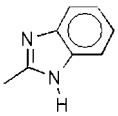
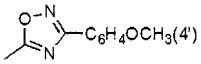
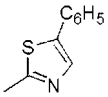


Compound RTI-4229-	X	R	IC_{50}, nM (K_i, nM) DA [^{3}H]WIN 35,428	NE [^{3}H]Nisoxetine	5-HT [^{3}H]Paroxetine	NE/DA* Ratio	5-HT/DA* Ratio
Cocaine	—	—	89.1	3298 (1986)	1045 (45)	37	12
WIN 35,065-2	H		23	920 (554)	2000 (182)	40	87
334	Cl	—C_2H_5	0.50	120 (72)	3090 (281)	240	6180
165	Cl	—CH_3	0.59	181 (109)	572 (52)	307	970
171	CH_3	—CH_3	0.93	254 (153)	3820 (348)	273	4110
335	Cl	—$CH(CH_3)_2$	1.19	954 (575)	2320 (216)	801	1950
177	Cl	—C_6H_5	1.28	504 (304)	2420 (220)	394	1890
346	Cl	—$C_6H_4OCH_3$(4′)	1.57	762 (454)	5880 (535)	485	3740
176	CH_3	—C_6H_5	1.58	398 (239)	5110 (465)	252	3230
354	CH_3	—C_2H_5	1.62	299 (180)	6400 (582)	185	3950
347	Cl	—C_6H_4F(4′)	1.86	918 (553)	7256 (660)	494	3901
386	CH_3	—$C_6H_4OCH_3$(4′)	3.93	756 (450)	4027 (380)	194	3600
336	Cl	—$C_6H_4CH_3$(4′)	4.09	1714 (1033)	5741 (522)	419	1171
366	CH_3	—$CH(CH_3)_2$	4.5	2523 (1550)	42,900 (3900)	561	9533
345	Cl	—C_6H_4CI(4′)	6.42	5290 (3790)	>76 000 (6910)	824	>11,800
387	CH_3	—C_6H_5F(4′)	6.45	917 (546)	>100 000 (9400)	141	>15,400
337	Cl	—$C(CH_3)_3$	7.31	6320 (3807)	36 800 (3346)	863	865
371	CH_3	—C_6H_4CI(4′)	8.74	>100,000 (60 200)	>100 000 (9090)	>11 400	>11 400

*Ratio of IC_{50} values.

Table 4. 3β-Phenyltropane 2β-Heterocyclic Analogs Selective for the DAT



Compound RTI-4229-	X	R	IC$_{50}$, nM (K$_i$, nM) DA [^{3}H]WIN 35,428	NE [^{3}H]Nisoxetine	5-HT [^{3}H]Paroxetine	NE/DA* ratio	5-HT/DA* ratio
cocaine			89	3298 (1986)	1045 (45)	37	12
WIN 35,065-2	H	CO_2CH_3	23	920 (554)	2000 (182)	40	87
470	Cl		0.094	1590 (994)	1080 (98)	16 900	11 500
202	Cl		1.37	403 (250)	1120 (202.1)	294	818
451	CH_3		1.53	476 (287)	7120 (647)	311	4700
439	CH_3		1.57	1320 (795)	>100 000 (>909)	841	>64 000
141	Cl		1.81	835 (503)	357 (32.4)	461	186
219	Cl		5.71	8560 (5157)	10 000 (909)	1500	1800

*Ratio of IC$_{50}$ values.

that differences in the rate at which cocaine is administered determine its ability to produce psychomotor sensitization and presumably the associated adaptation in the brains of rats. Thus, a clinical candidate should also show low sensitization. In addition, a long duration of action would be desirable. Volkow et al[24] used positron emission tomography (PET) studies to show that the rate of clearance for the relatively more potent methylphenidate was significantly slower than for cocaine and suggested that this could account for the much lesser abuse of methylphenidate than cocaine despite their otherwise similar pharmacological properties. Furthermore, in selecting a candidate for further development, it is preferable for the compound to be orally available and no more stimulatory than cocaine at peak doses. As a direct test of the compound's potential efficacy in humans, the compound should substitute for cocaine in animal models and should block cocaine self-administration in both rats and rhesus monkeys.

Table 5. In Vitro Toxicity Assays*

Mutagenicity
NovaScreen
Cytochrome, P450
Sheep Isolated Cardiac Purkinje Fibers
HERG (ChanTest)

*HERG indicates human ether-a-go-go-related gene.

In order to identify 3-phenyltropane analogs that possessed pharmacological properties suitable for further consideration, the compounds listed in Tables 1 to 4 were first evaluated for locomotor activity in mice[25] and cocaine discrimination in rats; several compounds were also tested in in vitro toxicity assays listed in Table 5. The 5 compounds listed in Tables 6 and 7 showed the most favorable overall balance of pharmacological properties and toxicity results. It is interesting to note that all 5 compounds are 3β-phenyltropane 2β-1,2-(isoxazole) analogs (see Table 3 for structures). Examination of the data in Table 6 shows that cocaine produced its greatest stimulation in hour 1, and that by hour 3 the effect was gone. In contrast, all 2β-1,2-(isoxazoles) had their largest effect in hours 2 to 4. The ED$_{50}$ values for the 2β-1,2-(isoxazoles) ranged from 0.9 mg/kg for RTI-354 to 12.8 mg/kg for RTI-386. RTI-176 and RTI-354 produced greater stimulation than cocaine in

Table 6. Percentage Change From Vehicle in Locomotor Activity in Mice (intraperitoneal) for Compounds Selected for Further Evaluation*

Compound	Dose mg/kg	Hour 1	Hour 2	Hour 3	Hour 4	ED_{50} in Peak Hour mg/kg	First Hour: Ratio to Cocaine
Cocaine	5.6	+5	–26	–53	–1	18.8	
	17	+179†	–7	–53	–26		
	56	+452†	+201†	–47	–24		
RTI-177	1	+11	+27	+45	+76	3.4	1.1
	3	+331†	+456†	+377†	+378		
	10	+513†	+402†	+485†	+924†		
RTI-176	1	+48	+139	+89	+154	2.5	1.2
	3	+244†	+369	+283	+329		
	10	+526†	+663†	+363	+141		
RTI-354	0.3	+34	+99	+173	–72	0.9	1.4
	1	+449†	+489†	+222	+48		
	3	+613†	+893†	+725†	+81		
RTI-336	1	+8	+44	–49	+170	3.9	0.7
	3	+23	+153	+265	+119		
	10	+308†	+1034†	+1024†	+493		
RTI-386	3	+73	+32	+27	+30	12.8	0.6
	10	+187†	+115†	+65	+34		
	30	+290†	+235†	+430†	+483†		

*Table adapted from Carroll et al.[25]

†Different from vehicle by Newman-Keuls following 1-way analysis of variance, $P < .05$.

their peak hours; RTI-177 had about the same stimulation as cocaine; and RTI-336 and RTI-386 were less stimulatory than cocaine.

All five 3β-(1,2-isoxazoles) selected for further evaluation showed full generalization to the cocaine cue (≥75% of rats choosing the cocaine lever), with the ED_{50} values ranging from 0.82 mg/kg for RTI-354 to 11.0 mg/kg for RTI-386; the ED_{50} for cocaine was 2.64 mg/kg.

3β-(4-Chlorophenyl)-2β̃ (3-phenylisoxazol-5-yl)tropane (RTI-177), which possessed ED_{50} values of 4.7 and 5.7 mg/kg in the locomotor activity and drug-discrimination test after oral administration (unpublished results, Carroll 2004) and also reduced cocaine self-administration after oral administration in a rat model of self-administration, was studied for its effect on cocaine self-administration in rhesus monkeys. Pretreatment intravenously (IV) with RTI-177 produced a dose-related reduction in cocaine self-administration in rhesus monkeys trained to self-administer cocaine (0.1 and 0.3 mg/kg) under a second-order schedule of IV drug delivery. The ED_{50} was 0.11 mg/kg, which is an order of magnitude more potent than

Table 7. Drug Discrimination Effects of Compounds Selected for Further Evaluation in Rats (intraperitoneal)*

	Percentage of Rats Choosing the Cocaine Lever											
Compound	0.1	0.17	0.3	0.56	1	1.7	3	5.6	10	17	30	ED_{50} mg/kg
Cocaine					21	32	59	82	97			2.64
RTI-177							29	63	75			4.73
RTI-176							0	75	86			4.88
RTI-354			0	14	75	100						0.82
RTI-336					14		14	50	88			5.95
RTI-386								0		43	83	11.00

*Table adapted from Carroll et al.[25]

Table 8. Relationship Between Reductions in Cocaine Self-administration and Dopamine Transporter Occupancy

	ED_{10}		ED_{50}	
Subject	**Dose mg/kg**	**Occupancy %**	**Dose mg/kg**	**Occupancy %**
GBR 12909				
ROu-4	0.74	*	1.20	62
RLk-4	0.61	*	1.32	68
	0.52	*	1.45	71
Average ± SD	0.62 ± 0.11	*	1.29 ± 0.13	67 ± 4.6
RTI-177				
RMk-3	0.09	*	0.14	77
RMv-3	0.05	*	0.09	73
RLk-4	0.05	*	0.10	68
Average ± SD	0.06 ± 0.02	*	0.11 ± 0.03	73 ± 4.5

*Occupancy values that were below the limit of detection.

GBR 12909, which has an ED_{50} of 1.29 mg/kg (Table 8).[26] PET neuroimaging studies revealed that the ED_{10} doses of RTI-177 and GBR 12909 resulted in DAT occupancies below the threshold (<10%) of detection, whereas ED_{50} doses resulted in DAT occupancies of 73% and 67%, respectively.[26] RTI-177 and GBR 12909 were substituted for cocaine in drug self-administration studies in order to characterize their reinforcing effects. Both RTI-177 and GBR 12909 reliably maintained drug self-administration at levels greater than those maintained by saline in all subjects (Figure 1). Moreover, the shape of the dose-effect curves resembled an inverted U-shape function typical of psychomotor stimulants. However, rates of responding were lower than those maintained by the training dose of cocaine (0.1 mg/kg/infusion) in 2 of 3 subjects substituted with GBR 12909 and in all 3 subjects substituted with RTI-177.

In acute toxicity studies in male rats, 3β-(4-chlorophenyl)-2β-[3-(4'-methylphenyl)isoxazol-5-yl]tropane (RTI-336) possessed an LD_{50} of 180 mg/kg after oral administration, compared with 49 mg/kg for RTI-177 (unpublished results, Howell 2005; Table 9). These results suggested that RTI-336 was a better candidate than RTI-177 for further preclinical development. Similar to RTI-177, RTI-336 showed oral activity in the locomotor activity and drug-discrimination test with ED_{50}s of 14.4 and 3.54 mg/kg, respectively. Of

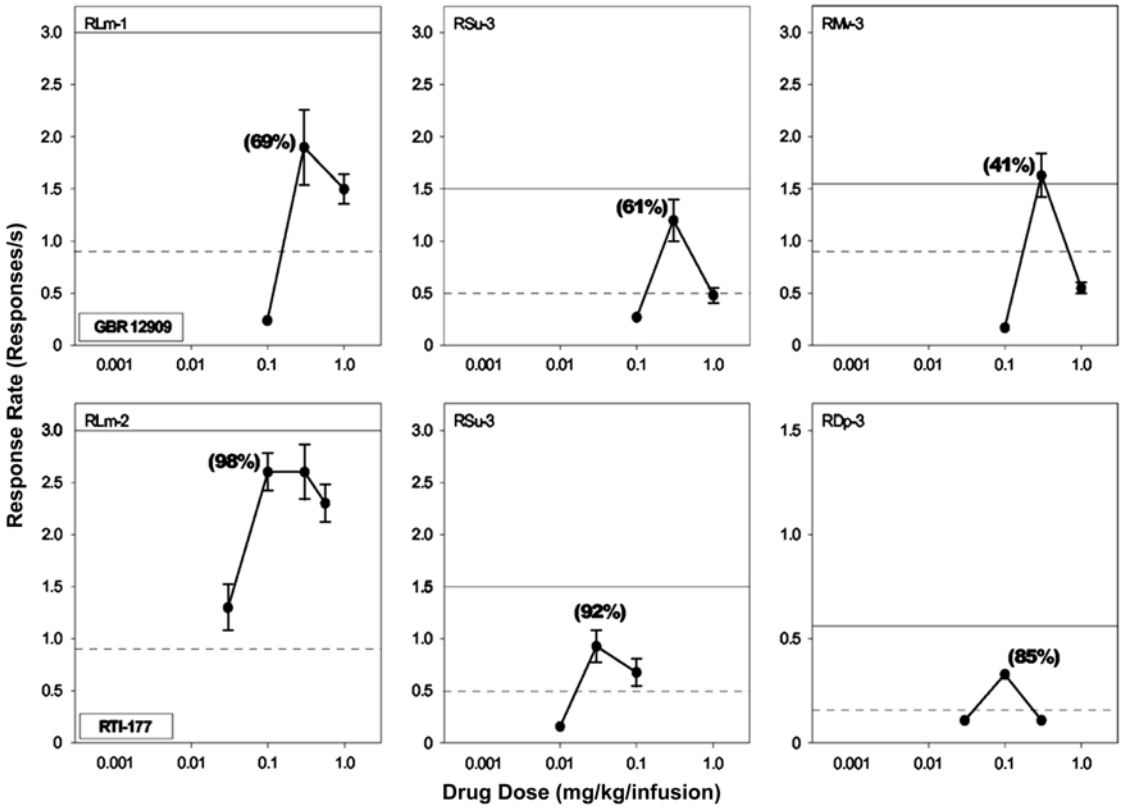


Figure 1. Self-administration of GBR 12909 and RTI-177. Response rates (responses per second) for GBR 12909 and RTI-177 as a function of drug dose under a second-order schedule of IV drug self-administration in individual subjects. The unbroken lines indicate mean rates of responding maintained by the training dose of cocaine (0.1 mg/kg/infusion). Dashed lines indicate the upper limit for responding during saline extinction. Each data point was determined on a single occasion and is the mean (±SD) of the last 5 sessions in a condition. Numbers in parentheses indicate percentage of DAT occupancy at doses that maintained peak rates of responding. Modified from Lindsey et al.[26]

Table 9. Comparison of ED_{50}/LD_{50} Values and Minimum Lethal Dose for RTI-177 and RTI-336*

RTI No.	Drug Discrimination and Lethality, Rat (PO) ED_{50} (mg/kg)	LD_{50} (mg/kg)	TI (LD_{50}/ED_{50})	Minimum Lethal, PO mg/kg
336	3.54	180	51	100
177	5.7	48.9	8.57	40-60

*PO indicates by mouth.

importance, RTI-336 showed very low sensitization relative to cocaine. RTI-336 reduced cocaine self-administration in a rat model of self-administration (unpublished results, Howell 2004), and in preliminary rhesus monkey studies, RTI-336 produced dose-dependent reductions in cocaine self-administration in 4 subjects and was equally effective at both maintenance doses of cocaine (0.1 and 0.3 mg/kg/injection). Food-maintained behavior was suppressed at the same doses of RTI-336 that suppressed cocaine-maintained behavior. Positron emission tomography (PET) imaging was conducted in the same subjects to determine the level of DAT occupancy associated with behaviorally-relevant doses of RTI-336. Doses of RTI-336 that reduced cocaine-maintained behavior by 50% (ED_{50}) resulted in 90% DAT occupancy for the group of 4 subjects. Daily food intake, body weight, and behavior were normal.

CONCLUSION

In summary, RTI-336 showed locomotor activity less than that of cocaine with no sensitization. It was orally active in both the locomotor assay in mice and drug discrimination tests in rats and possessed an excellent therapeutic ratio. RTI-336 reduced cocaine self-administration in both rat and rhesus monkey models and showed slow onset and long duration of action in rodent and monkey models. These preliminary studies in rhesus monkeys showed that RTI-336 was effective in suppressing cocaine self-administration at doses that had no obvious adverse behavioral effects. Varying the maintenance dose of cocaine had no influence on the effectiveness of drug pretreatments. There was no evidence of selective reductions in cocaine self-administration compared with food-maintained behavior. High levels of DAT occupancy were required to produce robust reduction in cocaine use.

ACKNOWLEDGMENTS

This research was supported by the National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, grant No. DA05477.

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