

Cocaine Antagonists; Studies on Cocaine Self-Administration

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Editorial

A series of recent studies by Dr. Jonathan Katz demonstrated preclinical efficacy of several compounds functioning as a cocaine antagonist using a drug self-administration procedure in rats. For example, 1) the atypical dopamine uptake inhibitors (Figure 1) JHW 007, AHN 2-005 [1,2], and RTI-371 [3], and 2) the σ R antagonist (Figure 2) rimcazole and its analogues SH 3-24 and SH 3-28 [4], all were able to shift dose-effect curves of cocaine self-administration down in a dose-dependent fashion when pre-treated.

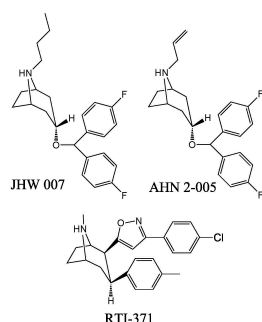


Figure 1: Chemical structures of atypical dopamine uptake inhibitors. AHN2-005, N-allyl-3 α -[bis(4'-fluorophenyl)methoxy]-tropane; JHW 007, N-(n-butyl)-3 α -[bis-(4'-fluorophenyl)methoxy]-tropane; RTI-371, 3 β -(4-methylphenyl)-2 β -[3-(4-chlorophenyl)isoxazol-5-yl]tropane.

Their dose-dependent insurmountable antagonism of cocaine self-administration was relatively specific because comparable responding maintained by presentations of food pellets was insensitive to active doses of these compounds that decreased maximal responding maintained by cocaine injection [1-4]. The pattern of antagonism was similar to effects of the μ -opioid agonist methadone on heroin self-administration since methadone can also produce a dose-dependent insurmountable antagonism of heroin self-administration [5]. On the other hand, none of them maintained self-administration responding above vehicle levels when substituted cocaine [1,3,4], d-methamphetamine, heroin or ketamine [5]. However, the pattern of substitution was different from that of methadone since methadone can substitute for heroin or d-methamphetamine [5]. An excellent review article recently discussed potential mechanisms underlying their action as a cocaine antagonist [6]. There are several relatively viable mechanisms underlying their cocaine-antagonist effect.

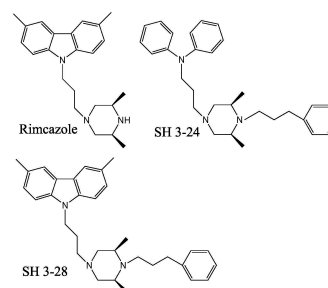


Figure 2: Chemical structures of σ R antagonists. Rimcazole, 9-[3-(cis-3,5-dimethyl-1-piperazinyl)propyl]-9H-carbazole; SH 3-24, [3-(cis-3,5-dimethyl-4-[3-phenylpropyl]-1-piperazinyl)-propyl]diphenylamine; SH 3-28, 9-[3-(cis-3,5-dimethyl-4-[3-phenylpropyl]-1-piperazinyl)-propyl]carbazole.

Dopamine Transporter (DAT)/ σ R Dual Inhibition

Pretreatment with standard dopamine uptake inhibitors alone (Figure 3) shifted the dose-effect curves of cocaine self-administration to the left (i.e. potentiation) in a dose-dependent manner [1,3,4,7,8] while that of σ R antagonists was virtually without effects on cocaine self-administration [4,9-11].

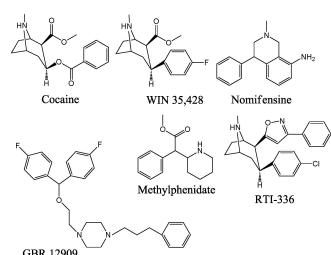


Figure 3: Chemical structures of standard dopamine uptake inhibitors. Cocaine; GBR 12909, 1-(2-[bis(4-fluorophenyl)methoxy]ethyl)-4-(3-phenylpropyl)piperazine; methylphenidate; nomifensine; RTI-366, 3 β -(4-chlorophenyl)-2 β -[3-(4-methylphenyl)isoxazol-5-yl]tropane; WIN 35,428; (—)-3 β -(4-fluorophenyl)-tropan-2 β -carboxylic acid methyl ester tartrate.

However, pretreatment with a σ R antagonist dose-dependently shifted down dose-effect curves of cocaine self-administration when combined with a standard dopamine uptake inhibitor [4]. Thus it appears that DAT/ σ R dual inhibition can result in an insurmountable antagonism of reinforcing effects of cocaine. Interestingly all above-

referenced compounds function as a cocaine antagonist except RTI-371, which also have considerable affinity to the DAT as well as σ 1Rs (Table 1) relative to the standard dopamine uptake inhibitors except RTI-336.

Compound	DAT K_i [[³ H]WIN 35,428]	σ_1 K_i [[³ H](+)-Pentazocine]	σ_2 K_i [[³ H]DTG]
Cocaine	76.6 ^a (72.6 - 80.5)	5,190 ^a (3,800 - 7,060)	19,300 ^a (16,000 - 23,300)
AHN 2-005	8.82 ^b (8.13-9.56)	15.5 ^b (13.2-18.3)	28.5 ^b (23.6-34.4)
JHW 007	12.0 ^c (11.2-12.8)	2.40 ^b (2.07-2.80)	12.0 ^b (10.0-14.4)
Methylphenidate	65.8 ^d (61.2 - 70.8)	6,780 ^d (4,520 - 10,200)	37,400 ^d (21,200 - 66,100)
Nomifensine	21.0 ^d (18.9 - 23.3)	8,240 ^d (5,360 - 12,700)	65,200 ^d (54,300 - 78,300)
RTI-336	10.8 ^e (8.27-14.0)	5,180 ^e (3060-8780)	365 ^e (21.4-6220)
RTI-371	7.81 ^e (6.93-8.79)	15,800 ^e (10,100-24,900)	353 ^e (187-665)
Rimcazole	96.6 ^d (77.3 - 121)	883 ^d (661 - 1,180)	238 ^d (171 - 329)
SH 3-24	12.2 ^d (10.8 - 13.8)	22.9 ^d (18.5 - 28.2)	20.0 ^d (15.7 - 25.6)
SH 3-28	188 ^d (166 - 213)	19.0 ^d (15.3 - 23.6)	47.2 ^d (40.4 - 55.2)
WIN 35,428	5.24 ^{†, d} (4.92 - 5.57)	5,700 ^d (4,060 - 8,020)	4,160 ^d (3,120 - 5,550)

^aGarcés-Ramírez et al. (2011) [12]

^bHiranita et al. (2014a) [5]

^cKopajtic et al. (2010) [13]

^dHiranita et al. (2011) [4]

^eHiranita et al. (2014b) [3]

†The value for affinity of WIN 35,428 at the DAT is K_d values obtained from homologous competition studies. The values reported for all compounds were determined using identical assay conditions.

Table 1: Inhibition by various compounds of specific binding to the DAT and σ_1 , or σ_2 receptors. The values listed are K_i values (nM) with SEM or 95% confidence limits in parentheses.

However, the atypical dopamine uptake inhibitor RTI-371 and the standard dopamine uptake inhibitor RTI-336 both commonly have high affinity to the DAT as well as σ_2 Rs, and low affinity to σ_1 Rs (Table 1) and their effects on cocaine self-administration were quite different since pretreatment with RTI-336 potentiated cocaine self-administration [3]. Therefore, these findings suggest that σ_1 Rs are responsible for the DAT/ σ R dual inhibition of cocaine self-administration. However, due to quite low affinity of RTI-371 to σ_1 Rs, DAT/ σ_1 R dual inhibition appears to be sufficient but is not essential for induction of a cocaine-antagonist action.

Differences in Kinetic Variables

Studies on in vivo binding to DAT demonstrated slower apparent rates of occupancy with the DAT by several cocaine antagonists AHN 2-005, JHW 007, and RTI-371 relative to the standard dopamine uptake inhibitors cocaine, GBR 12909 or RTI-336 [3,14-16]. Thus the slower association rates with DAT might result in a cocaine-antagonist action. However, a study introduced several atypical dopamine uptake inhibitors with fast association rates with DAT in mice [17]. Therefore, it appears that the slower association rates with DAT are not essential for induction of a cocaine-antagonist action, either.

Conformational Differences in DAT Binding

Studies evaluating accessibility of the sulfhydryl-reactive reagent [2-(trimethylammonium)ethyl]-methanethiosulfonate to an inserted cysteine (I159C), which is accessible when the extracellular DAT gate is open but inaccessible when it is closed, indicated that cocaine and its analogue WIN 35,428 bind an open DAT conformation to synapse clefts (outward-facing conformation), whereas several atypical dopamine uptake inhibitors (AHN 2-005, and JHW 007) bind a closed conformation (inward-facing conformation) [5,18]. Thus binding to the inward-facing conformation appeared to be important for a cocaine-antagonist action. However, as with cocaine, it was shown that the cocaine antagonist RTI-371 and the standard dopamine uptake inhibitor RTI-336 both bind the outward-facing conformation of the DAT. Further, as with JHW 007, the standard dopamine uptake inhibitor GBR 12909 was found to bind the inward-facing conformation [5]. Therefore the conformational differences in DAT are again not prerequisite for induction of a cocaine-antagonist action, either.

In summary, none of these hypotheses uniformly explained the cocaine-antagonist action. Thus it is likely that a cocaine-antagonist action can be generated from several pathways and there might be no uniform pathway to induce a cocaine-antagonist action. Nonetheless, future studies on a cocaine-antagonist action should result in development of medications for cocaine abuse. In addition, such studies would also contribute to identification of medications for attention-deficit hyperactivity disorder (ADHD) with lower potential of abuse since the typical dopamine uptake inhibitor methylphenidate (Ritalin[®]) is currently prescribed for ADHD patients. Actually the cocaine antagonist AHN 2-005 is currently under development as a potential medication for ADHD [19].

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