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DAT Conformation Does Not Predict the Ability of Atypical Dopamine Uptake Inhibitors to Substitute for Cocaine

Takato Hiranita*

Division of Neurotoxicology, National Center for Toxicological Research (NCTR), U.S. Food and Drug Administration (FDA), Jefferson, USA

Editorial

The reuptake inhibition of dopamine (DA) through the DA transporter (DAT) is thought to be the primary mechanism underlying the reinforcing effects of cocaine [1,2]. However, there are several DA reuptake inhibitors that do not produce appreciable cocaine-like effects *in vivo* [2–4]. Previously, there were several relatively viable hypotheses related to the mechanisms underlying the atypical effects of such agents, but new studies have decreased this number [3,5]. The new findings may contribute to the development of a better understanding of what constitutes cocaine-like behavioral effects.

It is well known that the DAT plays an important role in cocaine reinforcement. For example, cocaine has a relatively high affinity for the DAT [6]. Further, various DA reuptake inhibitors can maintain self-administration responding above vehicle levels when substituted for cocaine and potentiate cocaine self-administration when used as a pretreatment. These include standard DA reuptake inhibitors including WIN 35,428, methylphenidate and nomifensine [2,3,7–9]. However, several DA reuptake inhibitors are not reinforcing when substituted for cocaine and antagonize cocaine self-administration when used as a pretreatment. These include the atypical DA uptake inhibitors, JHW 007 and RTI-371 [2,3,7]. The attributes that contribute to their atypical effects as DA reuptake inhibitors are unknown but there are several relatively viable hypotheses that address this issue [10,11]. One of such hypotheses is that conformational differences may affect DAT binding.

Studies evaluating the accessibility of the sulfhydryl-reactive reagent [2-(trimethylammonium)ethyl]-methanethiosulfonate to an internal cysteine residue of the DAT (I159C), which is only accessible when the extracellular DAT gate is open, have indicated that cocaine and its analogue WIN 35,428 bind to an open DAT conformation at synaptic clefts (the ‘outward-facing’ conformation), whereas several atypical DA reuptake inhibitors (e.g. JHW 007) bind to the ‘closed’ or ‘inward-facing’ conformation [10,12]. Thus, binding to the inward-facing conformation appears to be important for the atypical effects of these agents. In contrast to cocaine, JHW 007 was shown to be inactive in locomotor activity

***Corresponding author:** Takato Hiranita, Division of Neurotoxicology, National Center for Toxicological Research (NCTR), U.S. Food and Drug Administration (FDA), 3900 NCTR Road, Jefferson, AR 72079-9501, USA, Tel: 870-543-6823; Fax: 870-543-7745; takato.hiranita@fda.hhs.gov.

assessments and cocaine discrimination and self-administration procedures (Table 1). Both RTI-371 and RTI-336 bind to the outward-facing conformation of the DAT (Table 1), but only RTI-336 substituted for cocaine using cocaine self-administration procedures (Table 1). A more recent study assessed whether preference for the DAT conformation is predictive of the cocaine-like behavioral effects of various novel DA reuptake inhibitors using locomotor activity assessments and cocaine discrimination procedures (Table 1). Among a series of novel compounds [LX-10, -11, -12, 13, -16, -19, -21, -22, -23 and -24 in Table 1, assumedly synthesized by Lifen Xu (LX), one of the authors] that have been shown to preferentially bind to the outward-facing conformations of the DAT, only LX-10 was cocaine-like in both behavioral assessments. In contrast, six LX compounds (LX-11, -12, -21, -22, -23 and -24) were inactive in both assessments. In addition, LX-13, -16 and -19 stimulated locomotor activity but did not fully substitute for cocaine using cocaine discrimination procedures. Thus, the conformation of the DAT is not a viable determinant of the production of cocaine-like behavioral outcomes.

In summary, new findings suggest that the conformation of the DAT is not predictive of the behavioral effects of DA reuptake inhibitors. Differences in kinetic variables and DAT/σ-receptor dual inhibition are two remaining relative viable hypotheses for addressing the mechanisms underlying the reduced cocaine-like effects of atypical DA reuptake inhibitors [10,11,13]. Future studies to explore these two hypotheses should facilitate the development of effective medication(s) for cocaine abuse.

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Table 1

Preference of the DAT conformation, effects on locomotor activity and substitution for cocaine under cocaine discrimination or self-administration procedures.

Compound [reference]	DAT conformation (μM)	Locomotor activity (μmol/kg, I.P.)	Substitution for cocaine in cocaine discrimination (μmol/kg, I.P.)	Substitution for cocaine in cocaine self-administration (mg/kg/injection, I.V.)
Cocaine [3,5]	Outward-facing (100)	Increased (30–100) Increased (20 or 40 mg/kg, I.P.)	Substituted (30)	Substituted (0.1 and 0.32)
JHW 007 [2,3]	Inward-facing (1)	Inactive (0.3–3.0 mg/kg, I.P.)	Not substituted (0.17–5.6 mg/kg, I.P.)	Not substituted (0.032–1.0)
RTI-336 [3]	Outward-facing (1)	Increased (10–56 mg/kg, I.P.)	Substituted (56 mg/kg, I.P.)	Substituted (0.1 and 0.32)
RTI-337 [3]	Outward-facing (1)	Increased (100 mg/kg, I.P.)	Partially substituted (10–100 mg/kg, I.P.)	Not substituted (0.1–3.2)
LX-10 [5]	Outward-facing (10)	Increased (3 and 10)	Substituted (10)	N.T.
LX-11 [5]	Outward-facing (20)	Inactive (3–56)	Not substituted (17)	N.T.
LX-12 [5]	Outward-facing (20)	Inactive (3–300)	Not substituted (0.3–10)	N.T.
LX-13 [5]	Outward-facing (10)	Increased (10 and 30)	Not substituted (3–17)	N.T.
LX-15 [5]	No change (20)	Inactive (3–100)	Not substituted (0.3–10)	N.T.
LX-16 [5]	Outward-facing (10)	Increased (3–100)	Partially substituted (0.3–3)	N.T.
LX-19 [5]	Outward-facing (10)	Increased (30–100)	Partially substituted (0.3–10)	N.T.
LX-20 [5]	No change (20)	Inactive (30)	Not substituted (0.3–3)	N.T.
LX-21 [5]	Outward-facing (10)	Inactive (0.56–170)	Not substituted (0.3–3)	N.T.
LX-22 [5]	Outward-facing (20)	Inactive (0.56–300)	Not substituted (0.3–10)	N.T.
LX-23 [5]	Outward-facing (10)	Inactive (0.56–56)	Not substituted (0.3–5.6)	N.T.
LX-24 [5]	Outward-facing (20)	Inactive (1.7–56)	Not substituted (0.3–5.6)	N.T.

NT: Not Tested