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Identification of Antagonists Selective for Sigma Receptor Subtypes that are Active *In vivo*

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Editorial

Two antagonists that are active *in vivo* and selective for the sigma receptor (σ R) subtypes, σ_1 and σ_2 , have very recently been described [1]. It is anticipated that these antagonists will contribute to the development of σ R pharmacology and medication discovery for stimulant abuse [1].

σ Rs have been mischaracterized [2–4] and were initially thought to be opioid receptor subtypes [5]. They have been classified into two subtypes based on specific radioligand binding assays using [3 H](+)-pentazocine for σ_1 Rs and [3 H]1,3-di-*o*-tolylguanidine ([3 H]DTG), in the presence of (+)-pentazocine to mask the σ_1 R, for σ_2 Rs [6–11] (Table 1). The σ_1 R has already been cloned and is a 25–29 kDa intracellular chaperone protein composed of 223 amino acids [12–14]. In contrast, the [3 H](+)-pentazocine-inaccessible σ R, the σ_2 R, is an 18–21 kDa protein that has not yet been cloned. Until recently, there have been no reports of antagonists that are selective for either receptor subtype or that are active *in vivo*, probably because of the lack of reliable *in vivo* assays for σ R subtypes. The paper by Katz et al. [1] finally identifies antagonists selective for σ R subtypes [1] that are active *in vivo*.

In this report [1] that utilized radioligand binding and drug self-administration procedures, σ R ligands that were self-administered by cocaine-experienced subjects were classified as σ R agonists whereas compounds that failed to maintain self-administration responding above vehicle levels in cocaine-experienced subjects and blocked the self-administration of σ R agonists were classified as antagonists. Radioligand binding assays demonstrated that 3-(2-(azepan-1-yl)ethyl)-6-(3-fluoropropyl)benzo[d]thiazol-2(3H)-one hydrochloride (CM 304) is 567-fold more selective for σ_1 than for σ_2 receptors (Table 1). In contrast, 1-(4-(6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)butyl)-3-methyl-1H-benzo[d]imidazol-2(3H)-one hydrochloride (CM 398) is 331-fold more selective for σ_2 than σ_1 receptors (Table 1). Behavioral studies in rats trained to self-administer cocaine (0.32–1.0 mg/kg/injection, i.v.)

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were used to assess whether these two ligands could antagonize self-administration of σ R agonists [1].

For example, pretreatment with the selective σ_1 R ligand CM 304 (0.32–3.2 mg/kg, i.p.) dose-dependently decreased the maximal rate of self-administration responding and the highest dose of CM 304 flattened the inverted U-shaped dose-effect curves for self-administration of the selective σ_1 R agonist 2-(4-morpholinethyl)-1-phenylcyclohexanecarboxylate hydrochloride (PRE-084, 0.032–1.0 mg/kg/injection, i.v.). In addition, the same range of CM 304 doses also produced dose-dependent insurmountable antagonism of the self-administration of the σ_1 R agonist (+)-pentazocine (0.032–1.0 mg/kg/injection, i.v.) as well as the non-selective $\sigma_{1/2}$ R agonist DTG (0.1–3.2 mg/kg/injection, i.v.). In contrast, pre-treatment with the selective σ_2 R ligand CM 398 (up to 3.2 mg/kg, i.p.) was without effects on self-administration of PRE-084 or (+)-pentazocine. However, CM 304 (0.1–1.0 mg/kg, i.p.) dose-dependently produced insurmountable antagonism of DTG self-administration. Thus, the σ_1 R-selective CM 304 blocked self-administration of all three σ R agonists. However, self-administration of the non-selective $\sigma_{1/2}$ R agonist DTG only was sensitive to the σ_2 R-selective CM 398.

In summary, antagonists selective for σ R subtypes have been identified. These antagonists will be useful as experimental tools for studies of σ R pharmacology. For example, using CM 304 as a selective σ_1 R antagonist, it has been demonstrated that σ_1 Rs are potential treatment targets for stimulant abuse [1]. Further, reports have implicated σ_1 Rs in various biological functions and drugs acting at these receptors have been studied for their therapeutic effects in cancer, HIV infection, psychiatric disorders, and substance abuse [2–4,15]. Thus, the use of these newly-identified, selective and biologically active ligands will contribute to the understanding of σ R-related disorders.

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References

1. Katz JL, Hiranita T, Kopajtic TA, Rice KC, Mesangeau C, et al. Blockade of Cocaine or Sigma Receptor Agonist Self-Administration by Subtype- Selective Sigma Receptor Antagonists. *J Pharmacol Exp Ther*. 2016; 358:109–124. [PubMed: 27189970]
2. Katz JL, Su TP, Hiranita T, Hayashi T, Tanda G, et al. A Role for Sigma Receptors in Stimulant Self Administration and Addiction. *Pharmaceuticals (Basel)*. 2011; 4:880–914. [PubMed: 21904468]
3. Katz JL, Hong WC, Hiranita T, Su TP. A role for sigma receptors in stimulant self-administration and addiction. *Behav Pharmacol*. 2016; 27:100–115. [PubMed: 26650253]
4. Hiranita T. Identification of the Sigma-2 Receptor: Distinct from the Progesterone Receptor Membrane Component 1 (PGRMC1). *J Alcohol Drug Depend*. 2016; 4:e130.
5. Martin WR, Eades CG, Thompson JA, Huppler RE, Gilbert PE. The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. *J Pharmacol Exp Ther*. 1976; 197:517–532. [PubMed: 945347]
6. Hellewell SB, Bruce A, Feinstein G, Orringer J, Williams W, et al. Rat liver and kidney contain high densities of sigma 1 and sigma 2 receptors: characterization by ligand binding and photoaffinity labeling. *Eur J Pharmacol*. 1994; 268:9–18. [PubMed: 7925616]

7. Hiranita T, Soto PL, Kohut SJ, Kopajtic T, Cao J, et al. Decreases in cocaine self-administration with dual inhibition of the dopamine transporter and sigma receptors. *J Pharmacol Exp Ther*. 2011; 339:662–677. [PubMed: 21859929]
8. Hiranita T, Mereu M, Soto PL, Tanda G, Katz JL, et al. Self-administration of cocaine induces dopamine-independent self-administration of sigma agonists. *Neuropsychopharmacology*. 2013; 38:605–615. [PubMed: 23187725]
9. Hiranita T, Soto PL, Tanda G, Kopajtic TA, Katz JL. Stimulants as specific inducers of dopamine-independent sigma agonist self-administration in rats. *J Pharmacol Exp Ther*. 2013; 347:20–29. [PubMed: 23908387]
10. Hiranita T, Wilkinson DS, Hong WC, Zou MF, Kopajtic TA, et al. 2-isoxazol-3-phenyltropane derivatives of cocaine: molecular and atypical system effects at the dopamine transporter. *J Pharmacol Exp Ther*. 2014; 349:297–309. [PubMed: 24518035]
11. Garcés-Ramírez L, Green JL, Hiranita T, Kopajtic TA, Mereu M, et al. Sigma receptor agonists: Receptor binding and effects on mesolimbic dopamine neurotransmission assessed by microdialysis in rats. *Biol Psychiatry*. 2011; 69:208–217. [PubMed: 20950794]
12. Hanner M, Moebius FF, Flandorfer A, Knaus HG, Striessnig J, et al. Purification, molecular cloning, and expression of the mammalian sigma1-binding site. *Proc Natl Acad Sci USA*. 1996; 93:8072–8077. [PubMed: 8755605]
13. Hayashi T, Su TP. Sigma-1 receptor chaperones at the ER-mitochondrion interface regulate Ca(2+) signaling and cell survival. *Cell*. 2007; 131:596–610. [PubMed: 17981125]
14. Chu UB, Mavlyutov TA, Chu ML, Yang H, Schulman A, et al. The Sigma-2 Receptor and Progesterone Receptor Membrane Component 1 are Different Binding Sites Derived From Independent Genes. *EBioMedicine*. 2015; 2:1806–1813. [PubMed: 26870805]
15. Maurice T, Su TP. The pharmacology of sigma-1 receptors. *Pharmacol Ther*. 2009; 124:195–206. [PubMed: 19619582]

Table 1

Affinities of various compounds for binding to σ_1 or σ_2 receptors, as well as subtype selectivity (ratio of σ_2/σ_1 binding). The values listed are K_i values (nM) with 95% confidence limits in parentheses.

Compound	σ_1R ($[^3H]$ (+)-pentazocine)	σ_2R ($[^3H]$ DTG in the presence of (+)-pentazocine)	σ_2/σ_1
CM 304 [1]	0.684 (0.552–0.847)	388 (215–702)	567
CM 398 [1]	1,490 (1,200–1,860)	4.50 (2.78–7.27)	0.00302
DTG [11]	57.4 (49.3–66.7)	21.9* (14.8–32.4)	0.382
(+)-Pentazocine [9]	4.59* (4.26–4.97)	224 (195–257)	48.8
PRE-084 [11]	53.2 (44.8–63.2)	32,100 (23,100–44,700)	603