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Editorial Open Access

# 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 (σR) subtypes, $\sigma_1$ and $\sigma_2$, have very recently been described [1]. It is anticipated that these antagonists will contribute to the development of σR pharmacology and medication discovery for stimulant abuse [1].

σRs 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 $\sigma_1$Rs and [$^3$H]1,3-di-*o*-tolylguanidine ([$^3$H]DTG), in the presence of (+)-pentazocine to mask the $\sigma_1$R, for $\sigma_2$Rs [6-11] (Table 1). The $\sigma_1$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 σR, the $\sigma_2$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 σR subtypes. The paper by Katz et al. [1] finally identifies antagonists selective for σR subtypes [1] that are active *in vivo*.

In this report [1] that utilized radioligand binding and drug self-administration procedures, σR ligands that were self-administered by cocaine-experienced subjects were classified as σR agonists whereas compounds that failed to maintain self-administration responding above vehicle levels in cocaine-experienced subjects and blocked the self-administration of σR 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 $\sigma_1$ than for $\sigma_2$ 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 $\sigma_2$ than σ1 receptors (Table 1). Behavioral studies in rats trained to self-administer cocaine (0.32-1.0 mg/kg/injection, i.v.) were used to assess whether these two ligands could antagonize self-administration of σR agonists [1].

For example, pretreatment with the selective $\sigma_1$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 $\sigma_1$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 σ1R 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 $\sigma_2$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 $\sigma_1$R-selective CM 304 blocked self-administration of all three σR agonists. However, self-administration of the non-selective $\sigma_{1/2}$R agonist DTG only was sensitive to the $\sigma_2$R-selective CM 398.

In summary, antagonists selective for σR subtypes have been identified. These antagonists will be useful as experimental tools for studies of σR pharmacology. For example, using CM 304 as a selective σ1R antagonist, it has been demonstrated that σ1Rs are potential treatment targets for stimulant abuse [1]. Further, reports have implicated σ1Rs 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 σR-related disorders.

| Compound | $\sigma_1$R ([$^3$H](+)-pentazocine) | $\sigma_2$R ([3H]DTG in the presence of (+)-pentazocine) | $\sigma_2/\sigma_1$ |
|---|---|---|---|
| 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 |

**Table 1:** Affinities of various compounds for binding to $\sigma_1$ or $\sigma_2$ receptors, as well as subtype selectivity (ratio of $\sigma_2/\sigma_1$ binding). The values listed are Ki values (nM) with 95% confidence limits in parentheses.

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