

# *N,N*-dimethyltryptamine (DMT) as an Endogenous Ligand Candidate for the Sigma-1 Receptor 660.10

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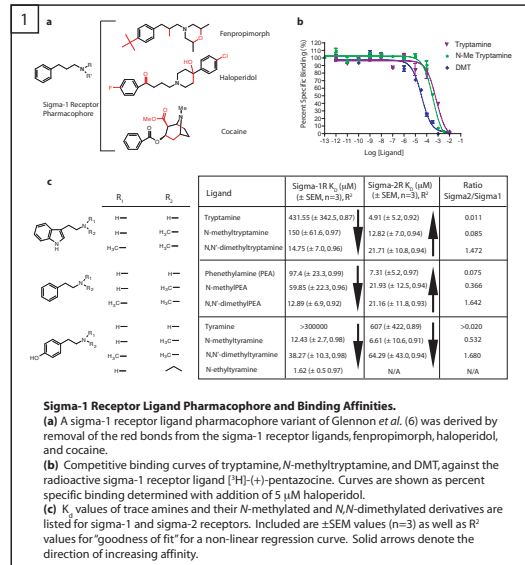
## ABSTRACT

The sigma-1 receptor is widely distributed in the central nervous system and periphery. Originally mischaracterized as an opioid receptor, the sigma-1 receptor binds to a vast number of synthetic compounds but does not bind opioid peptides; it is currently considered an orphan receptor. The sigma-1 receptor pharmacophore includes an aralkylamine core, also found in the endogenous compound *N,N*-dimethyltryptamine (DMT). DMT acts as a hallucinogen, but its receptor targets have remained unclear. DMT bound to sigma-1 receptors and inhibited voltage-gated Na<sup>+</sup> channels in both native cardiac myocytes and heterologous cells that express sigma-1 receptors. DMT induced hypermobility in wildtype mice but not in sigma-1 receptor knockout mice. These biochemical, physiological, and behavioral experiments indicate DMT as an endogenous agonist for the sigma-1 receptor.

## INTRODUCTION

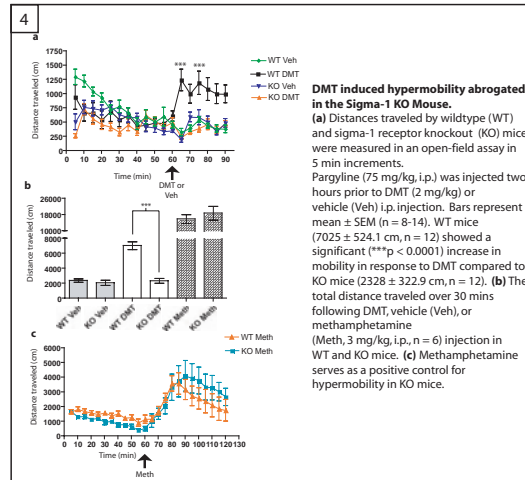
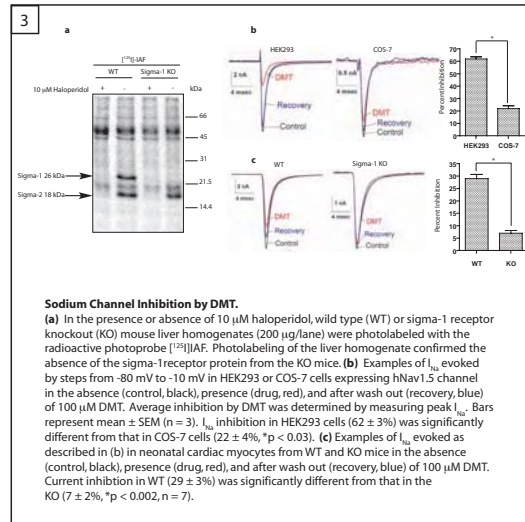
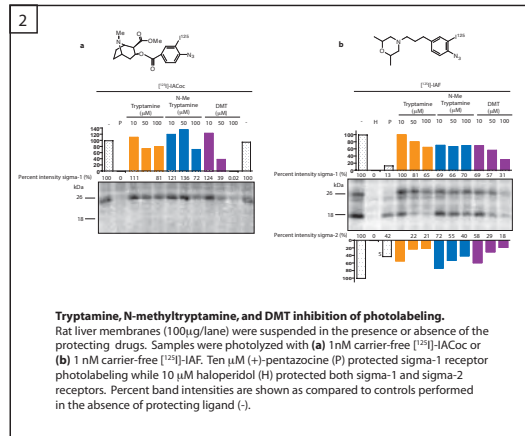
The sigma-1 receptor binds a broad range of synthetic compounds (1). It has long been suspected that the sigma-1 receptor is targeted by endogenous ligands and several candidates have been previously proposed (2, 3). Although progesterone and other neuroactive steroids, for example, are known to bind and regulate some sigma-1 receptor functions (1, 4), they do not show agonist properties on ion channels in electrophysiological experiments (5).

Our search for sigma receptor endogenous ligand(s) was based on a variant of the canonical sigma-1 receptor ligand pharmacophore (6), but is more basic in structure. Otherwise dissimilar sigma-1 receptor ligands possess a common *N*-substituted pharmacophore: an *N,N*-dialkyl or *N*-alkyl-*N*-aralkyl product, most easily recognized in the high affinity sigma-1 receptor ligand, fenpropimorph (7). Similar chemical backbones can be derived from other sigma-1 receptor ligands such as haloperidol and cocaine. *N*-substituted trace amines harbor this sigma-1 receptor ligand pharmacophore, but their interactions with sigma receptors have not been determined. Of particular interest is the only known endogenous mammalian *N,N*-dimethylated trace amine, *N,N*-dimethyltryptamine (DMT) (8-10). In addition to being one of the active compounds in psychoactive snuffs (*yopo*, *epena*) and sacramental teas (*ayahuasca*, *yage*) used in native shamanic rituals in South America, DMT can be produced by enzymes in mammalian lung (11) and in rodent brain (12). DMT has been found in human urine, blood, and cerebrospinal fluid (9, 13). While there are no conclusive quantitative studies measuring the abundance of endogenous DMT due to its rapid metabolism (14), DMT concentrations can be localized and elevated in certain instances. Evidence suggests that DMT can be localized by active transport into brain vesicles and that DMT production increases in rodent brain under environmental stresses (8). Although a family of G protein-coupled receptors (GPCRs) known as the trace amine receptors (TAR) has been discovered in 2001 (15), only two members of this family respond to trace amines and have been renamed to trace amine-associated receptors (TAARs) (16). Because other binding targets for trace amines and DMT are likely (8), we first examined the sigma-1 receptor binding affinities of the trace amines and their *N*-methylated and *N,N*-dimethylated counterparts.



### Sigma-1 Receptor Ligand Pharmacophore and Binding Affinities.

(a) A sigma-1 receptor ligand pharmacophore variant of Glennon et al. (6) was derived by removal of the red bonds from the sigma-1 receptor ligands, fenpropimorph, haloperidol, and cocaine. (b) Competitive binding curves of tryptamine, *N*-methyltryptamine, and DMT, against the radioactive sigma-1 receptor ligand [<sup>3</sup>H]-(+)-pentazocine. Curves are shown as percent specific binding determined with addition of 5 μM haloperidol. (c) K<sub>i</sub> values of trace amines and their *N*-methylated and *N,N*-dimethylated derivatives are listed for sigma-1 and sigma-2 receptors. Included are ±SEM values (n=3) as well as R<sup>2</sup> values for 'goodness of fit' for a non-linear regression curve. Solid arrows denote the direction of increasing affinity.



## CONCLUSIONS

- The binding, biochemical, physiological, and behavioral studies reported here all support the hypothesis that DMT acts as a ligand for the sigma-1 receptor. Based on our binding results and the sigma-1 receptor pharmacophore, endogenous trace amines and their *N*-methyl and *N,N*-dimethyl derivatives are likely to serve as endogenous sigma receptor regulators. These studies suggest that this natural hallucinogen could exert its action by binding to sigma-1 receptors, which are abundant in the brain (1, 17).
- Some behavioral actions of DMT depend on the sigma-1 receptor, which may provide an alternative research area for psychiatric disorders unexplained by dopamine, serotonin, or glutamatergic systems.
- DMT, the only known mammalian *N,N*-dimethylated trace amine, can activate the sigma-1 receptor to modulate Na<sup>+</sup> channels.
- The recent discovery that the sigma-1 receptor functions as a molecular chaperone (18) may be relevant as sigma-1 receptors may serve as a molecular chaperone for ion channels. Furthermore, the behavioral effect of DMT may be due to activation or inhibition of sigma-1 receptor chaperone activity instead of, or in addition to, DMT inhibition of ion channels via the sigma-1 receptor.
- This discovery may also extend to *N,N*-dimethylated neurotransmitters such as the psychoactive serotonin derivative, *N,N*-dimethylserotonin (bufotenine), which has been found at elevated levels in the urine of schizophrenic patients (10).
- The finding that DMT and sigma-1 receptors act as a ligand-receptor pair provides a possible connection that will enable researchers to elucidate the biological functions of both of these molecules.

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