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9-(Aminomethyl)-9,10-dihydroanthracene is a novel and unlikely 5-HT_{2A} receptor antagonist

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Abstract

Structural elaboration of phenylethylamine to 9-(aminomethyl)-9,10-dihydroanthracene (AMDA) produces an agent with high affinity (K_i = 9.5–21 nM) at 5-HT_{2A} receptors. It was shown that AMDA acts as a 5-HT_{2A} receptor antagonist. The structure and molecular geometry of AMDA are not consistent with existing pharmacophore models for 5-HT_{2A} receptor antagonist activity. Thus, AMDA may be a structurally novel parent of a new class of 5-HT_{2A} receptor antagonists that binds to the receptor in a unique fashion that is distinct from the binding topology of existing 5-HT_{2A} receptor antagonists.

Keywords: 5-HT receptor; 5-HT_{2A} receptor antagonist

The serotonin (5-hydroxytryptamine; 5-HT) receptor family consists of a large number (> 14) distinct entities that have been identified using cloning technology. Many therapeutically useful drugs have 5-HT receptors as their targets (Roth, 1994; Glennon et al., 1999). Specifically, 5-hydroxytryptamine$_2$ (5-HT_2) receptors have been implicated as the site of action of hallucinogens, atypical antipsychotic drugs and certain atypical antidepressants (Roth, 1994; Glennon et al., 1999). Additionally, 5-HT_2 receptors are important for processes as diverse as uterine and vascular smooth muscle function, platelet aggregation and central nervous system function (Glennon et al., 1999). For these reasons, generation of structurally novel agents that interact with 5-HT_2 receptors has been of considerable current interest (Glennon and Dukat, 1997). The contemporary process of drug discovery can make use of protein sequence data, information from site-directed mutagenesis, and evaluation of hypothetical 3-dimensional graphics models coupled with classical, intuition-driven structural modification of active, lead compounds. The 5-HT_{2A} receptor sequences point to a number of conserved aromatic amino acid residues that have been shown to be important for ligand binding and receptor function (Roth et al., 1998). Molecular models based on the 5-HT_{2A} receptor sequences and the low resolution projection structure of rhodopsin have been used to visualize ways in which existing and designed compounds may interact with multiple aromatic residues within the ligand binding site (Glennon et al., 1999).

Typically, simple unsubstituted phenylethylamines show very low affinity for 5-HT_2 receptors (e.g., phenylethylamine, 5-HT_{2A} K_i > 10,000 nM). Some time ago, examination of receptor models suggested that the affinity of structures containing a phenylethylamine skeleton could be enhanced by introducing a second aromatic moiety, perhaps by participating in additional aromatic–aromatic interactions between ligand and receptor (Westkaemper et al., 1992). This prompted us to prepare and evaluate 5-aminomethyl-10,11-dihydro-5-*H*-dibenzo[*a*,*d*]cycloheptadiene (Fig. 1, **1**) which proved to have modest but enhanced affinity (K_i = 220 nM; Westkaemper et al., 1992) at ketanserin-labeled sites compared to the bicyclic compound containing a single aromatic ring (Fig. 1, **2**, K_i > 10,000 nM). A logical extension of this structural theme is incorporation of two aromatic rings fused to a central six-membered structure such as 9-(aminomethyl)-9,10-dihydroanthracene (Fig. 1, AMDA). This structural modification induces small changes in the geometric relationship

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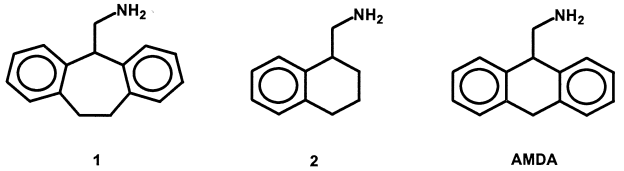

Fig. 1. Chemical structures of 5-aminomethyl-10,11-dihydro-5-*H*-dibenzo[*a*,*d*]cycloheptadiene (**1**), 1-aminomethyl-1,2,3,4-tetrahydronaphthalene (**2**), and 9-(aminomethyl)-9,10-dihydroanthracene.

between the two aromatic rings and was thus an attempt to determine the configuration that is optimal for ligand affinity. We now report the characterization of AMDA as a high-affinity 5-HT_{2A} receptor antagonist.

AMDA (Fouché, 1970) was synthesized from 9,10-dihydroanthracene-9-carboxylamide (Davis et al., 1964) by reduction with borane-tetrahydrofuran. Ligand binding assays using [^{3}H]ketanserin and [^{3}H]1-(4-bromo-2,5-dimethoxyphenyl)-2-aminnopropane ([^3H]DOB), and phosphoinositide (PI) hydrolysis assays were performed as previously described (Roth et al., 1997). K_i values are reported as means of 2–3 separate determinations.

Introduction of the second aromatic ring into compound **2**, conceptually equivalent to contraction of the central ring of **1**, significantly enhances affinity of AMDA at both ketanserin-labeled ($K_i = 21 \pm 2.1$ nM) and DOB-labeled ($K_i = 9.5 \pm 5$ nM) 5-HT_{2A} sites. Since **2** has no measurable affinity to the 5-HT_{2A} receptor ($K_i > 10{,}000$ nM; Westkaemper et al., 1992), the enhanced affinity for both **1** at ketanserin-labeled ($K_i = 112 \pm 4.2$ nM) and DOB-labeled ($K_i = 39 \pm 27$ nM) 5-HT_{2A} receptors, and AMDA is most likely due to the presence of the second aromatic ring, not simply due to the elaboration of the central cycloheptane or cyclohexane rings. The observation that AMDA has approximately 4- to 5-fold higher affinity for 5-HT_{2A} sites than **1**, suggests that the geometric relationship between the aromatic rings presented in AMDA is more optimal than that for **1**, but this issue will require further study.

Typically, antagonists have comparable affinities for both antagonist labeled (ketanserin) and agonist labeled (DOB) 5-HT_{2A} sites. Agonists, on the other hand, have at least several fold higher affinity for DOB vs. ketanserin labeled sites. The $K_{i,ketanserin}/K_{i,DOB}$ ratio of approximately 2 suggests that AMDA may be an antagonist. To determine whether AMDA is an agonist or antagonist, dose-response studies for PI hydrolysis were performed using stably transfected 3T3 cells expressing the 5-HT_{2A} receptor. Dose-response studies show that AMDA is devoid of agonist activity up to a dose of 10,000 nM while 5-HT behaved as an agonist with a K_{act} of 53 ± 16 nM. The K_{act} value for 5-HT is similar to that previously obtained by ourselves (Roth et al., 1997). Inhibition studies showed that 10 μM AMDA nearly completely (80%) inhibited the ability of 10 μM 5-HT to activate PI hydrolysis. These preliminary results suggest that AMDA is an antagonist at 5-HT_{2A} receptors.

Several pharmacophore models for 5-HT_{2A} receptors have been proposed based on the structure–activity relationships of known antagonists (see Glennon and Dukat, 1997 for a review). Typically, the essential geometric characteristics are described by the distances between two aromatic functionalities ($d_3 = 4.6$–7.3 Å) and the distances between each aromatic ring and the basic amine nitrogen ($d_1 = 5.2$–8.4 Å, $d_2 = 5.7$–8.5 Å). The corresponding dimensions for the minimum energy conformation of AMDA are similar to existing agents with respect to the aromatic rings ($d_3 = 4.9$ Å) but deviate substantially in that it is not symmetrical with respect to the two amine-ring distances ($d_1 = 3.5$ Å, $d_2 = 5.2$ Å), d_1 being much shorter than is considered optimal.

AMDA is a high affinity antagonist for the 5-HT_{2A} receptor. This is remarkable because it was conceptually derived by modification of substructures with no measurable affinity for the receptor. Comparison of the geometric parameters of AMDA with structure–activity relationships formulated from typical antagonists suggest that AMDA may bind at the receptor in a fashion that is different from known antagonists. This, coupled with the fact that there is little structural resemblance between AMDA and known serotonergic antagonists, suggests that AMDA may be the first member of a structurally novel class of compounds that seems to bind to the receptor in a manner distinct from classical 5-HT_{2A} receptor antagonists. It is anticipated that structural elaboration of the AMDA may generate 5-HT_{2A} receptor antagonists with novel pharmacological properties.

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