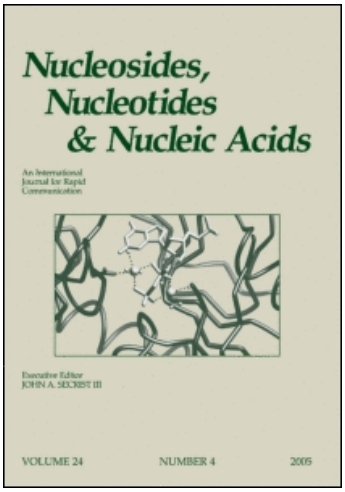

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Characterization of the Binding of a Novel Non-Xanthine Adenosine Antagonist Radioligand, [^{3}H]CGS 15943, to Multiple Affinity States of the Adenosine A_1 Receptor in the Rat Cortex

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CHARACTERIZATION OF THE BINDING OF A NOVEL NON-XANTHINE ADENOSINE ANTAGONIST RADIOLIGAND, [^{3}H]CGS 15943, TO MULTIPLE AFFINITY STATES OF THE ADENOSINE A_1 RECEPTOR IN THE RAT CORTEX

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The use of xanthine adenosine receptor antagonists such as 1,3-dipropyl-8-phenylxanthine (DPX) as radioligands for the characterization of adenosine receptor pharmacology have been limited by their high lipophilicity, low specific activity, and their general lack of selectivity and affinity for adenosine receptors[1]. Recent attempts to address the technical problems associated with this class of compounds has resulted in the development of several xanthine derivatives (e.g.the functionalized xanthine congeners [^{3}H]XCC and [^{3}H]XAC[2], and [^{3}H]CPX[3]) which bind with high and selective affinity to the adenosine A_1 receptor subtype. Based on efforts to optimize non-xanthine adenosine receptor antagonists[4], CGS 15943, a derivative of the pyrazoloquinazoline benzodiazepine receptor inverse agonist CGS 8216[5], represents the first reported non-xanthine structure that potently blocks adenosine receptors[6]. CGS 15943 has nanomolar affinity for both A_1 and A_2 receptor subtypes[6]. However, in contrast to many of the xanthine adenosine receptor antagonists, CGS 15943 is not a phosphodiesterase inhibitor and does not interact with adenosine transporter sites[6]. This compound is a potent and selective adenosine receptor antagonist *in vivo*[7] with a solubility/affinity ratio of greater than 1000[7]. In the present studies, the binding of [^{3}H]CGS 15943 to the adenosine A_1 receptor was characterized.

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Ligand saturation experiments revealed the [^{3}H]CGS 15943 labeled a single class of recognition sites with high affinity (Kd = 4 nM) and limited capacity (Bmax = 1.5 pmol/mg protein). Competition experiments revealed that the binding of [^{3}H]CGS 15943 was consistent with the labeling of the A_1 receptor subtype. Adenosine agonists inhibited 1 nM [^{3}H]CGS 15943 binding with the following potency order: CPA (IC_{50} = 15 nM) > 2-CADO > R-PIA > NECA > S-PIA > CGS 21680 > CV 1808 (IC_{50} > 10,000 nM). The potency order for adenosine antagonists was CGS 15943 (IC_{50} = 5 nM) > 8-PT > PACPX > DPX > theophylline = caffeine (IC_{50} > 10,000 nM). Antagonist inhibition curves were steep and best described by a one-site binding model. In contrast, A_1 agonist competition curves were shallow. Computer analysis revealed that these inhibition curves were best described by a two-site binding model. Agonist competition curves generated in the presence of 1 mM GTP resulted in a rightward shift and steepening of the inhibition-concentration curves while antagonist binding was not affected. The complex binding interactions found with adensoine agonists indicate that [^{3}H]CGS 15943 labels both high and low affinity components of the adenosine A_1 receptor in the rat cortex. Thus [^{3}H]CGS 15943 represents the first radiolabeled non-xanthine adenosine antagonist which can be used to characterize multiple affinity states of the brain A_1 receptor.

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