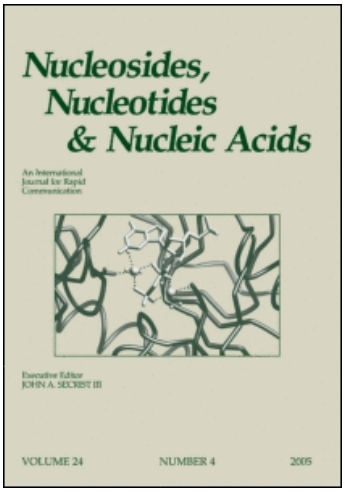

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APEC, AN A_2-SELECTIVE ADENOSINE AGONIST, IS A MORE POTENT LOCOMOTOR DEPRESSANT THAN N^6-CYCLOHEXYLADENOSINE

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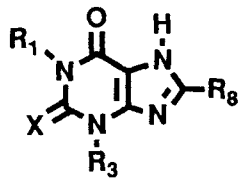
Abstract: The locomotor depressant effects of APEC are due to activation of central A_2 adenosine receptors, while the depressant effects of NECA are dependent primarily on A_1-receptor activation. A variety of potent A_1-antagonists, including conjugates of the XAC, were screened as antagonists; 2-thio-CPX and CPT reversed effects of CHA, but not of APEC.

Adenosine agonists, such as the A_1-selective CHA (N^6-cyclohexyladenosine) and the non-selective NECA (5'-N-ethylcarboxamidoadenosine) acting via a central mechanism, cause a dramatic depression of locomotor activity in mice. This depression is effectively reversed by non-selective adenosine antagonists, such as caffeine and theophylline, but not by the peripherally acting sulfo-xanthines.[1] An amine-functionalized congener, APEC, 2-[(2-aminoethylamino)-carbonylethylphenylethylamino]-5'-N-ethylcarboxamidoadenosine, a derivative of CGS21680,[2] is a potent, centrally active locomotor depressant in mice,[3] and its *in vitro* and *in vivo* pharmacology is consistent with A_2-selectivity.

Drugs were administered i.p. in a saline/emulphor mixture (4:1), 10 min before monitoring, in a computerized activity monitor (Digiscan® animal activity monitor, Omnitech Electronics, Columbus OH). Horizontal activity and total distance traveled were studied.[3]

From dose response curves for horizontal activity, it was found that APEC (ED_{50} 12 μg/kg) is more potent than CHA (ED_{50} 60 μg/kg) and less potent than NECA (ED_{50} 2 μg/kg). The locomotor depression by APEC was reversible by theophylline, but not by the peripheral antagonist 8-p-sulfophenyltheophylline (8-PST), suggesting a central mechanism of action.

In an effort to classify the receptor subtype mediating the depressant effects of APEC, various A_1-selective antagonists (Table) were screened as antagonists of the locomotor effects of adenosine agonists. 8-Cyclopentyl-1,3-dipropyl-2-thioxanthine (2-thio-CPX, 480-fold A1-



R_1 and R_3 = $(CH_2)_2CH_3$, and X = O, unless noted.

TABLE: Locomotor activity in mice injected with CHA (1 μmol/kg) alone or followed by a xanthine (10 mg/kg) after 10 min.[3] Horizontal activity and total distance travelled are expressed as counts per 30 min, with percent change from control in parentheses. R_8 is given for each xanthine.

CHA + xanthine	n=	H.A.	T.D.
control (no drug)	22	6315 (0%)	3344(0%)
CHA alone	6	803 (↓87±19%)	210 (↓94±51%)
H ($R_1 = R_2 = CH_3$)	15	7341 (↑16±2%)	6732(↑101±20%)
cyclopentyl ($R_1 = R_2 = CH_3$, X=S)	11	2503 (↓60±10%)	1971 (↓41±10%)
cyclopentyl (X=S) = **2-thio-CPX**	11	5448 (↓14±2%)	4530 (↑35±9%)
-ϕ-OCH_2COOH = **XCC**	8	2872 (↓55±11%)	1839 (↓45±15%)
-ϕ-$OCH_2CONH(CH_2)_2OH$	14	1901 (↓70±14%)	1081 (↓68±22%)
-ϕ-$OCH_2CONH(CH_2)_2NH$-----H = **XAC**	11	5729 (↓9±3.5%)	4374 (↑31±10%)
" -----$COCH_2$-ϕ-NH_2 = **PAPA-XAC**	12	4812 (↓24±4%)	4018 (↑20±7%)
" -----CSNH-ϕ-F_5	8	3322 (↓47±15%)	1648 (↓51±20%)
" -----$(COCH_2NH)_2$-Cbz	6	2470 (↓61±7%)	1119 (↓67±9%)

selective in binding assays)[4] was found to be active centrally, as an antagonist of CHA (1 μmol/kg). Against APEC at the ED50, neither 2-thio-CPX nor the A_1-selective antagonist 8-cyclopentyltheophylline (CPT)[5] influenced locomotor depression. This indicated that APEC acts in vivo through A_2-adenosine receptors. Also, CPT was found to completely reverse the locomotor effects of NECA at the ED50, suggesting that the action of NECA is primarily through A_1-adenosine receptors.

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