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Behavioural effects of selective A_2 adenosine receptor antagonists, CGS 21197 and CGS 22706, in mice

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THE present data show that selective A_2 adenosine receptor antagonists tended to increase locomotor and rearing activities in mice confronted with a free exploratory test. These findings support the hypothesis that the behavioural effects of adenosine antagonists can be linked to their actions at adenosine A_2 receptors.

Key words: CGS 21197, CGS 22706, Adenosine A_2 receptor antagonists, Locomotion, Rearing behaviour, Mice

Introduction

Although the central stimulant actions of adenosine receptor antagonists have been found to correlate with their capacity to compete with radioligands binding to adenosine A_1 receptors,[1] more recent data suggest that the A_2 receptor subtype may be responsible for these effects.[2–6] Recently we demonstrated that the first reported nonxanthine adenosine A_1 and A_2 antagonist, CGS 15943A, but not the highly selective, competitive A_1 receptor antagonist DPCPX, was able to increase the locomotor activity of mice confronted with a free exploratory test in a dose-dependent manner.[7] Thus, it was of interest to examine the behavioural effects of drugs which are highly selective adenosine A_2 antagonists such as CGS 21197 (5-amino-8,9-dihydro-2-(2-furanyl)-7H-cyclopenta [c] [1,2,4] triazolo [1, 5-c] pyrimidine) (IC_{50}=92nM) and CGS 22706 (5-amino-10-dimethylamino-2-(2-furanyl)-[1,2,4] triazolo [1, 5-c] quinazoline – bis mesylate) (IC_{50}=13nM). Since A_2 receptors are highly localized within dopamine-rich brain areas such as the striatum and nucleus accumbens,[8,9] the results of the present study are consistent with the view that adenosine is probably involved in dopamine related locomotor behaviours, insofar as we actually observed an increase of these activities following administration of adenosine A_2 receptor antagonists.

Methods

Animals: Male Swiss albino mice from 'Centre d'Elevage R. Janvier' (France), 12 weeks of age at time of testing, were used. Prior to experimental testing, they were housed five to a standard cage containing a constant supply of food pellets and water, and kept on a 12/12 h light/dark cycle with lights on at 1 a.m. in order to observe animals in their high activity period, that is when lights are off.

Drugs: Drugs were dissolved in saline with a drop of Tween 80 and administered intraperitonally, 30 min before testing, in concentrations giving an injection volume of 10 ml kg^{-1} body wt.

Statistical analysis: Statistical significance of differences between control and treated groups was ascertained by a combined analysis of variance and a Dunnett's (variances of means are assumed to be equal) or Bonferroni's (variances are not assumed to be equal) a posteriori *t*-test.

Apparatus: The apparatus consisted of a polyvinylchloride box (30×20×20 cm) covered with plexiglas and subdivided into six equal square exploratory units, which were all interconnected by small doors. It could be divided in half lengthwise by closing three temporary partitions. The apparatus was kept on a stand in the mouse room. The experimenter stood next to the box always at the same place.

Procedure: Approximately 24 h before testing, each subject was placed in one half of the apparatus with the temporary partitions in place so that it became familiarized with it. The floor of this half was covered with sawdust and the animal was given unlimited access to food and water. Next day, the subject was exposed to both familar and novel compartments by removal of the temporary partitions. It was then observed, in red light, for 10 min. The number of units entered (locomotion) and the number of rears made by the animals were recorded.

Mice were randomly allocated into the following groups; vehicle control (saline; n=20) and drugs(CGS 21197: 20 and 40 mg kg^{-1} in saline; n=10; CGS 22706: 5, 10, 15 and 20 mg kg^{-1} in saline; n=10).

Results

Analysis of variance revealed significant differences among the groups with respect to locomotion [$F(6,73) = 7.74$, $p < 0.001$] and rearing behaviour [$F(6,73) = 3.13$, $p < 0.008$]. Figure 1 shows that both drugs produced an increase in locomotion as well as in rearing behaviour. This latter effect was significant only with CGS 22706 at intermediate doses.

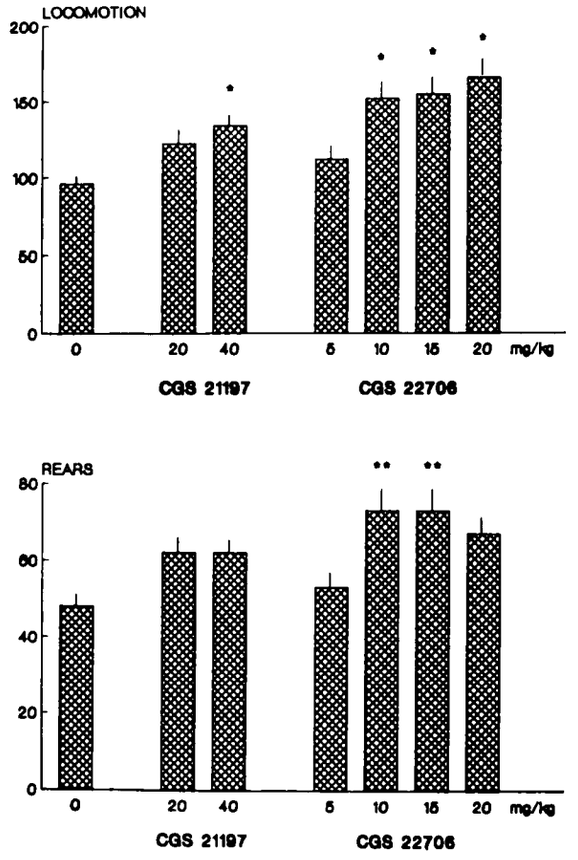

FIG. 1: Effects (means ± s.e.m.) of CGS 21197 and CGS 22706 on the locomotion and the number of rearings in a 10-min free exploratory test. $^{*}p < 0.05$, $^{**}p < 0.01$.

Discussion

The present results indicate that CGS 21197 and CGS 22706, two potent and selective adenosine A_2 receptor antagonists, increased locomotor activity and rearing behaviour in mice confronted with a free exploratory test. CGS 22706 significantly increased both of these behavioural parameters whereas CGS 21197 enhanced only locomotor activity. This discrepancy could be explained by the different antagonist affinities of CGS 21197 (IC_{50}=92nM) and CGS 22706 (IC_{50}=13nM) at the A_2 receptor subtype. The data obtained with CGS 21197 resemble those observed in our previous report with the non-selective adenosine A_1/A_2 receptor antagonist CGS 15943A which stimulated locomotor activity without affecting rearing behaviour.[7] Furthermore, CGS 22706, at the higher doses, failed to increase the number of rears significantly. This latter effect could be due to so-called 'response incompatibility'[10] since at this dose the animals exhibited intense and stereotyped locomotion that induced a general behavioural disorganization.

Since A_2 receptor blockade is associated with alterations in dopamine system function[8] and A_2 receptors are highly localized within dopamine-rich brain areas such as the striatum and nucleus accumben,[8,9] several authors have discussed the possible involvement of adenosine in dopamine related locomotor behaviours.[4,12,13]

Conclusion

The findings of the present study demonstrate that administration of selective adenosine A_2 receptor antagonists induced an increase of locomotor activity and rearing behaviour in mice confronted with a free exploratory test. These data as well as the lack of the highly selective adenosine A_1 receptor antagonist DPCPX[14] to increase locomotor activity in mice,[7] support the hypothesis that A_2 receptors modulate locomotor activity as recently suggested by several authors.[2–7]

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