Attenuated behavioral responses to acute and chronic cocaine in transgenic rats overexpressing adenosine 2A receptors

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INTRODUCTION

Cocaine's mechanism of action involves increases in dopamine (DA) neurotransmission within the mesolimbic circuitry of the brain followed by indirect activation of DA receptors, including D2 receptors. The recognition that D2 receptor stimulation (D2Rs), receptor agonists, have pharmacological and function distinct from its constituent receptors, has significantly expanded the range of potential drug targets and provided new avenues to develop novel drug addiction therapies. Recent functional assays indicated that cocaine produces D2 receptor-mediated conformational changes in the A2A/D2 receptor heteromer [1] while behavioral findings indicate that cocaine-induced locomotor and drug seeking behaviors may be influenced by A2A receptor stimulation [2,3].

AIM

The present study was designed to compare the effects of acute and chronic cocaine treatments in rats overexpressing A2A receptors and matched wild-type controls using sensitization and self-administration protocols.

METHODS

Animals

Male transgenic rats overexpressing human A2A receptor TGR(NSEhA2A) [4] and their wild-type controls (Sprague–Dawley rats, 250-300g, Charles River, Germany) were housed in standard laboratory conditions.

Drugs

Cocaine HCl (Sigma-Aldrich, USA) was dissolved in sterile 0.9% NaCl.

Locomotor activity measurement

The locomotor activity was monitored and quantified in experimental chambers (Dpto-Vainime, Columbus Instruments, USA) [5]. Interruptions of the photobeams (a 15x15 array located 3 cm from the floor surface) resulted in horizontal locomotor activity, defined as a distance traveled (expressed in cm). Measurements of locomotor activity began immediately after saline or cocaine injection and lasted 60 min.

Cocaine sensitization

Separate groups of rats were habituated in the experimental chambers for 2 days (2h/day) before the start of experiment. Next, rats overexpressing A2A receptors and matched wild-type controls were given cocaine (10 mg/kg, ip) or saline for 5 days in experimental chambers. Following a 2-day withdrawal (on day 10), rats were given a challenge dose of cocaine (10 mg/kg) in the experimental chambers.

Cocaine self-administration

Rats implanted with a silastic catheter in the external jugular vein were trained to self-administer cocaine (0.5 mg/kg/infusion) in a standard two-lever operant chambers (Med-Associates, Inc., USA). Under an increasing fixed-ratio (FR) schedule of cocaine reinforcement starting from (FR 1) on week 1, then FR 3 on week 2 and finally FR 5 on week 3, rats were given access to cocaine during 2h daily sessions performed 6 days/week (maintenance). Each completion of FR 1, FR 3 or FR 5 schedule on the “active” lever resulted in an infusion of cocaine (0.5 mg/kg) over 5 s. A tone and illumination of the stimulus light directly above the “active” lever (i.e. the drug-associated cue) was presented for 5 s, concurrently with a successful response for cocaine. Following each injection there was a 20 s time-out period during which responding was recorded, but had no programmed consequences [5].

Statistical analysis

All results are expressed as means±SEM. The data were analyzed using a Student’s t-test or a two-way analysis of variance (ANOVA) for repeated measure followed by post hoc Newman-Keuls test performed to locate differences between group means. The criterion for statistically significant differences was set at p<0.05.

SUMMARY

Cocaine sensitization

1) Slight lower spontaneous locomotor activity (1st day of habituation) and reduced basal locomotor activity (2nd day of habituation) in rats overexpressing A2A receptors, compared with wild-type animals were seen.

2) Acute administration of cocaine (10 mg/kg) resulted in ca. 80% increase in locomotion in wild-type rats, while no effect in animals overexpressing A2A receptors.

3) On day 10, a challenge dose of cocaine (10 mg/kg) evoked an increase (ca. 2.3- and 1.6-fold, respectively) in locomotor activity in wild-type controls and transgenic animals.

Self-administration

1) Under a FR 1 (week 1) rats overexpressing A2A receptors showed 24 active lever presses and 17 cocaine infusions and those values were significantly lower in comparison to wild-type animals exhibiting 38 active lever presses and 37 cocaine infusions.

2) Reduction in active lever presses (week 2, 76% and week 3, 77%) and cocaine infusions (week 2, 66% and week 3, 80%) was reported in rats overexpressing A2A receptors compared to wild-type controls.

3) Number of inactive lever presses was similar in both groups through all session days.

REFERENCES


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CONCLUSIONS

Our data indicate that the phenotype of rats overexpressing human A2A receptors indicates variations when compared with matched wild-type control rats. As compared to control animals, in transgenic rats, the basal locomotor activity is significantly decreased as well as acute cocaine produces attenuated locomotor response and its chronic administration has relatively weaker rewarding/reinforcing properties.