Role of adenosine (A)2A receptors in nicotine addiction– pharmacological and genetic aspects

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INTRODUCTION

Nicotine is a drug of abuse that elicits positive subjective effects in humans, strong withdrawal syndrome after its chronic use and relapses occurring even after long periods of abstinence [1]. In animal models it is self-administered, induces hyperlocomotion and behavioral sensitization [2] or can serve as a discriminative cue. The abuse of nicotine is linked to the enhancement of dopaminergic (DA) neurotransmission and indirect activation of DA D2 receptors in the brain mesolimbic system [3]. A number of data indicate antagonistic interaction between D2 and adenosine (A)2A receptors at the molecular and neurochemical levels. The interaction occurs in the striatum [4] and may have significance in controlling behavioral effects induced by nicotine [5].

AIM

The main goal of our experiment was to determine the role of A2A receptors in nicotine addiction. Firstly, we evaluated the effect of A2A receptor ligands (the agonist CGS 21680 and the antagonist KW 6002) on the development and expression of nicotine sensitization in wild-type (WT) rats. Secondly, we compared the effects of acute and chronic nicotine treatments in rats overexpressing A2A receptors using sensitization and nicotine-conditioned locomotion protocols.

METHODS

Animals

Male transgenic rats (TGR) overexpressing human A2A receptor [TGR(NSEhA2A)] and their WT controls (Sprague–Dawley rats) were housed in standard laboratory conditions.

Drugs

Nicotine bitartrate dihydrate (0.4 mg/kg, s.c.), KW 6002 (0.05-0.5 mg/kg, ip; -20 min), CGS 21680 (0.1-0.4 mg/kg,ip.;-5 min, ip) were used.

Locomotor activity measurement

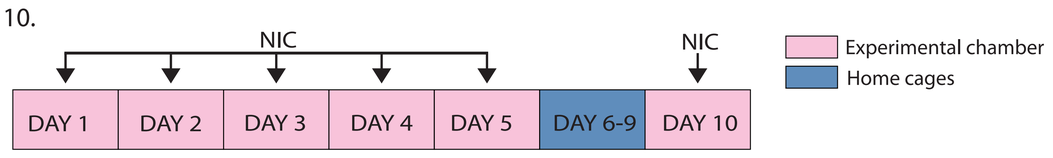
The locomotor activity was monitored and quantified in experimental chambers (Opto-Varimex, Columbus Instruments, USA). Interruptions of the photobeams (a 15x15 array located 3 cm from the floor surface) resulted in horizontal locomotor activity defined as a distance traveled (expressed in cm). Measurements of locomotor activity began immediately after vehicle or nicotine injections and lasted 60 min.

Basal locomotor activity

Animals were pretreated with either the appropriate vehicle, KW 6002 or CGS 21680 before the vehicle injection.

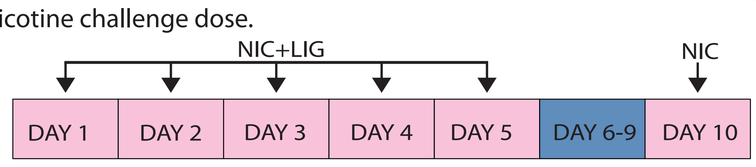
Nicotine sensitization

Sensitization was evoked by 5 daily injections of nicotine (0.4 mg/kg) and a challenge dose of the drug (0.4 mg/kg) on day 10.



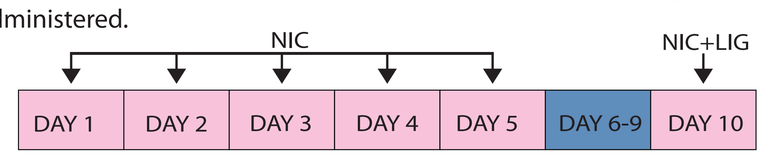
Development of nicotine sensitization

During the first 5 days, WT animals received the following injections: CGS 21680 (0.2-0.4 mg/kg) or KW 6002 (0.25-0.5 mg/kg) in combination with nicotine, while TGR were treated with vehicle or nicotine (0.4 mg/kg), then on days 6 to 9 the animals remained drug-free and were kept in home cages. On day 10, all the rats received the nicotine challenge dose.



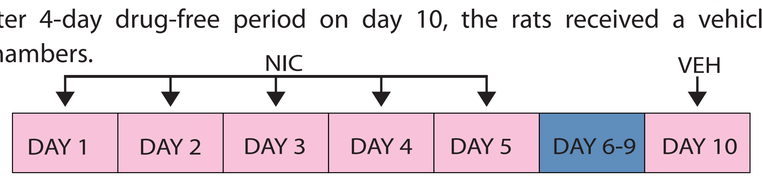
Expression of nicotine sensitization

The WT animals received repeatedly (5 first days) the vehicle or nicotine (0.4 mg/kg) while on day 10, they were pretreated by CGS 21680 (0.05-0.2 mg/kg) or KW 6002 (0.25-0.5 mg/kg) before a challenge dose of nicotine was administered.



Nicotine-Conditioned locomotion

Animals (WT and TGR) were given nicotine (0.4 mg/kg) or vehicle in home cages during the first 5 days of experiment. After 4-day drug-free period on day 10, the rats received a vehicle challenge injection in experimental chambers.



Statistical analysis

The data were analyzed using a one- or two-way analysis of variance (ANOVA), followed by post hoc Dunnett's test performed to locate the differences between group means. The criterion for statistically significant differences was set at $p<0.05$.

SUMMARY

1) During the development of nicotine sensitization CGS 21680 in the dose of 0.4 mg/kg (but not 0.2 mg/kg) given repeatedly with nicotine significantly ($p<0.05$) decreased the locomotor activity, while KW 6002 was inactive in this procedure.

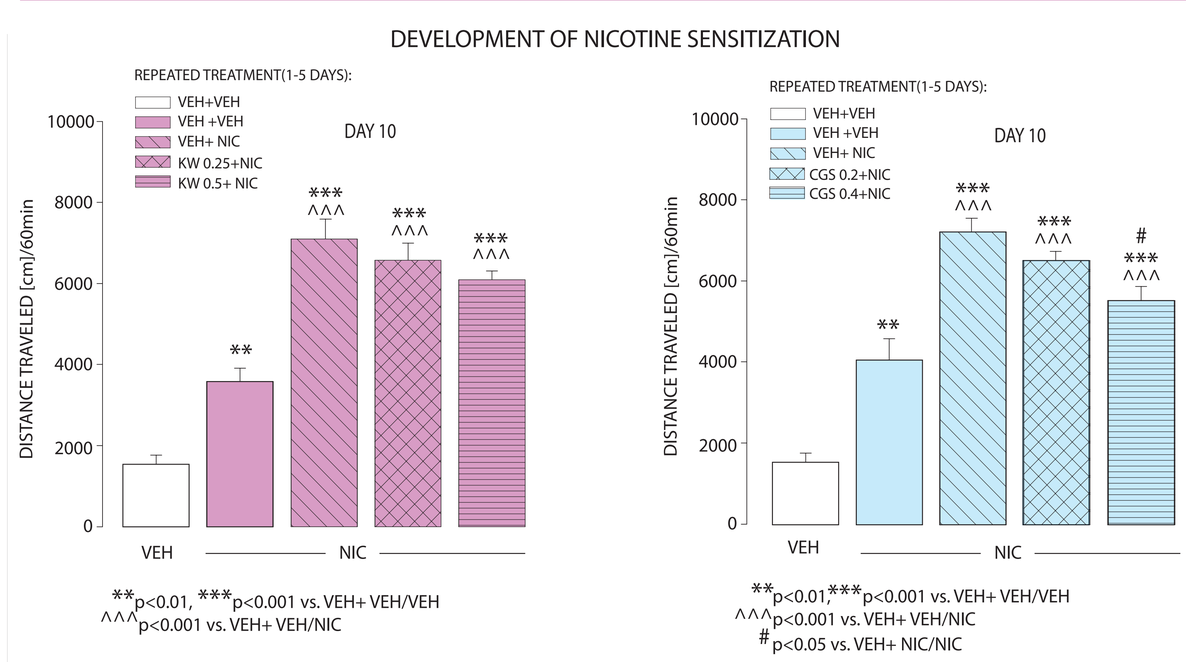
2) During the expression phase CGS 21680 (by 60% in a dose of 0.2 mg/kg, and by 55 % in a dose of 0.1 mg/kg) reduced the locomotor activity, whereas KW 6002 did not cause any changes.

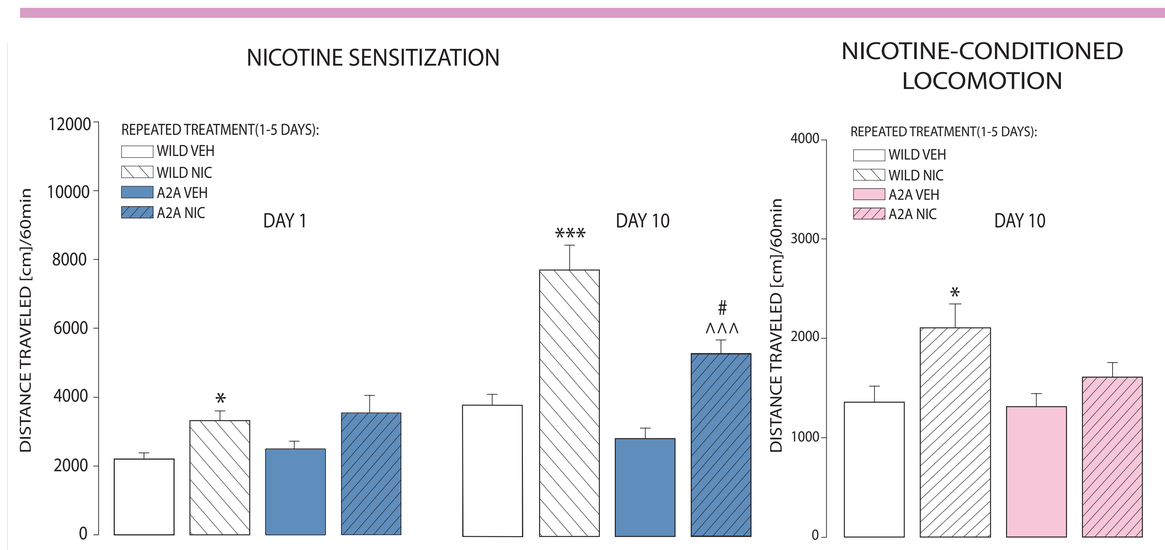
3) Both WT and TGR animals showed a 2-fold enhancement in the locomotor activity caused by repeated nicotine treatment.

4) WT rats (but not TGR animals) treated repeatedly (days 1 to 5) with nicotine and the vehicle on day 10 showed a significant enhancement in the locomotor activity in the environment associated with the administration of nicotine.

BASAL LOCOMOTOR ACTIVITY

Treatment	Horizontal distance traveled (cm)/60 min
Vehicle	1930±89
CGS 21680 (0.2mg/kg)	1523±241
CGS 21680 (0.4mg/kg)	776±83*
KW 6002 (0.25mg/kg)	1867±113
KW6002 (0.5mg/kg)	2568±468
*p<0.001 vs. vehicle	





CONCLUSIONS

Pharmacological stimulation of A2A receptors significantly decreases the behavioral response to acute and chronic nicotine treatment.

Rats overexpressing human A2A receptors did not show environment-triggered locomotion as the WT group did, despite the fact that they showed a similar response to nicotine sensitization.

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CONFLICT OF INTEREST

None

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