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Investigation of the Adenosine A(2A) Receptor on the Enhanced Rewarding Effects of Nicotine and Dopamine D2 Receptor Signaling in a Novel Heritable Model of Drug Abuse Vulnerability

Seth E. Turney
East Tennessee State University

Loren D. Peeters
East Tennessee State University

Olivia A. Jennings
East Tennessee State University

Liza J. Wills
East Tennessee State University

Russell W. Brown
James H. Quillen College of Medicine

Investigation of the adenosine A(2A) receptor on the enhanced rewarding effects of nicotine and dopamine D_2 receptor signaling in a novel heritable model of drug abuse vulnerability

Seth E. Turney, Loren D. Peeters, Olivia A. Jennings, Liza J. Wills, Russell W. Brown

Department of Biomedical Sciences, Quillen College of Medicine, East Tennessee State University, Johnson City, TN.

Introduction

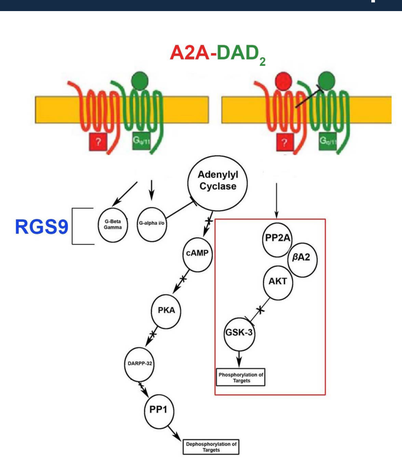
- Psychosis is a characteristic of several behavioral and neurological disorders, including schizophrenia, bipolar disorder, and obsessive-compulsive disorder [1].
- All of these disorders have presented with increases in dopamine D_2 (DAD_2) receptor sensitivity [2].
- Substance abuse comorbidity is common in all of these disorders, especially an increase in cigarette smoking [3].
- Disorders that present with increased DAD_2 sensitivity and substance abuse have a hereditary component [4].
- In past work, we have shown increases in DAD_2 sensitivity after neonatal quinpirole (DAD_2 agonist) to rats [5].
- We bred rats neonatally treated with quinpirole and tested the offspring. These offspring have shown increases in DAD_2 receptor sensitivity n this next (F1) generation [6].
- Since DAD_2 receptors form mutually inhibitory heteromers in the brain with adenosine A(2A) receptors, we analyzed whether an adenosine A(2A) agonist, CGS 21680, would block both enhanced responses to nicotine and sensorimotor gating deficits that occur in these animals.

Methods

- Rats neonatally treated with quinpirole HCl (1 mg/kg) or saline were grown to postnatal day 60 (P60) and bred. Their offspring were used as subjects.
- **Conditioned place preference (CPP):** a three chambered apparatus was used (See Figure 1).
- All rats were administered two initial drug-free preference tests on P41 and P42 to determine initial context preference.
- Conditioning began on P43 and ran through P50 (eight days total), with the dividers placed into the apparatus and the assignment of each context randomized across subjects.
- Conditioning consisted of two trials per day, an AM trial and a PM trial.
- AM session: All rats were IP administered saline and placed into their assigned context for a 10 min trial.
- PM session: All rats were IP administered saline or nicotine (0.6 mg/kg free base; SN) preceded by ip administration of saline (SS), or 0.09 mg/kg CGS 21680 (0.09CGS-N) and placed into the paired context for a 10 min trial.
- Post conditioning test was performed on P51 identical to pre-conditioning preference tests on P41-42.Dependent measure was the mean percent time spent in the paired context on the pre-conditioning trial subtracted away from mean percent time spent in the paired context on the post-conditioning test.
- **Prepulse Inhibition**: Each daily session began with a 5-minute habituation period with only background noise present (70 dB).
- Animals were administered three different, randomly-assigned trial types (*pulse, prepulse, no stimulus*). A *pulse* trial was a 120 dB startle pulse administered alone. A *Prepulse* trial was a stimulus 3, 6, or 12 dB above background noise. A *No stimulus trial a* stimulus was not presented. The response measured within a 250 ms window immediately following stimulus presentation.
- RGS9, β arrestin-2, and phospho-AKT were all analyzed with commercially available ELISA kits (Biomatik, Wilmington, DE; MyBioSource.com, San Diego, CA) in the dorsal striatum because it is heavily innervated by dopamine.
- **Table 1: Group Codes.**

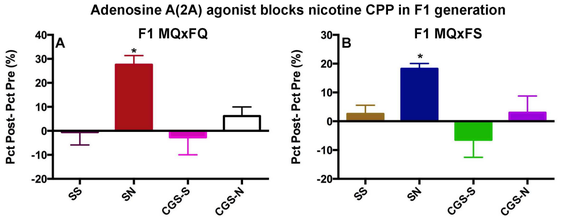
Treatment of Founders	Group Code
NQ Male (MQ), NQ Female (FQ)	F1 MQ x FQ
NQ Male (MQ), NS Female (FS)	F1 MQ x FS
NS Male (MS), NQ Female (FQ)	F1 MS x FQ
NS (Neonatal Saline)	F0 NS

Dopamine D2-A2A heteromer and pathway



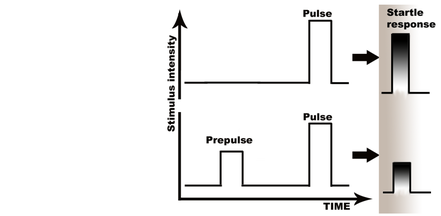
- Representation of the A2A-DAD2 pathway. In blue is RGS9, which is G-protein dependent; in red is the G-protein independent pathway

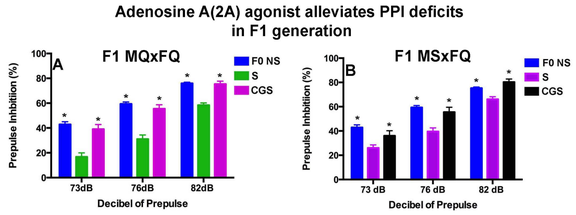
Figure 1. Nicotine CPP



- Both F1 groups MQxFQ and MQxFS conditioned with nicotine demonstrated significantly greater all other groups (indicated by *, p<.05).
- CGS 21680 (abbreviated with CGS) blocked nicotine CPP in both F1 MQxFQ and F1 MQxFS groups.

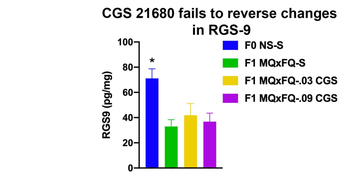
Figure 2. Sensorimotor gating test

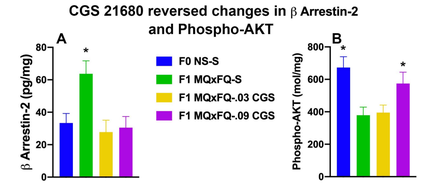




- A dose of 0.09 mg/kg CGS 21680 (CGS) alleviated deficits in PPI in both F1 MQxFQ and F1 MSxFQ groups. CGS groups were equivalent to controls (F0 NS) and greater than saline-treated F1 generation animals (indicated by *, p<.05).

Figure 3. Dopamine D_2 signaling in striatum





- All assays were performed in F1 generation MQxFQ rats.
- Top panel: Both doses of CGS 21680 (0.03 and 0.09 mg/kg) failed to reverse changes in RGS9 protein in F1 generation rats (* indicates F0 NS-S greater than all other groups, p<.05).
- Bottom panels: Both doses of CGS 21680 reversed changes in β arrestin-2 (*indicates F1 MQxFQ-S greater than all other groups, p<.05), and the .09 mg/kg CGS 21680 dose reversed changes in phospho-AKT (*indicated F0 NS-S and F1 MQxFQ-.09 CGS greater than all other groups, p<.05).

Conclusions

- Administration of the adenosine A(2A) agonist CGS 21680 reduced the enhanced response to nicotine in F1 generation offspring of NQ-treated rats.
- Likewise, administration of CGS 21680 was effective to alleviate PPI deficits in F1 generation offspring of NQ-treated rats.
- Both nicotine CPP and sensorimotor gating deficits share a common substrate: An increase in dopaminergic activity, especially in the forebrain.
- **These data suggest that treatment of both substance abuse comorbidity and psychosis may be a single pharmacological target, the adenosine A(2A) receptor.**
- Notably, there is a hypothesis that adenosine dysregulation precedes the changes in dopamine D_2 receptor sensitivity in schizophrenia, which has been termed the 'adenosine hypothesis of psychosis'[7].
- These results demonstrate that the adenosine A(2A) receptor is a potential target for the treatment of nicotine abuse comorbidity as well psychosis in behavioral disorders that present with increases in DAD_2 receptor sensitivity.
- Future studies will:
  1. Investigate the use of an adenosine A(2A) agonist as an adjunctive with an antipsychotic in behavioral tests with relevance to treatment of psychosis and substance abuse.
  2. Investigate neural plasticity markers involved in cell growth in brain areas heavily innervated by the dopamine neurotransmitter.

References

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