Published in final edited form as:
Neuropharmacology. 2009 June ; 56(8): 1082–1087. doi:10.1016/j.neuropharm.2009.03.005.

Activation of adenosine$_1$ (A_1) receptors suppresses head shakes induced by a serotonergic hallucinogen in rats

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Abstract

Modulation of glutamatergic neurotransmission by metabotropic glutamate2/3 (mGlu2/3) receptor agonists effectively treats seemingly diverse neuropsychiatric illness such as generalized anxiety disorder and schizophrenia. Activation of adenosine A_1 heteroceptors, like mGlu2 autoreceptors, decreases glutamate release in the medial prefrontal cortex (mPFC) and other limbic brain regions. Previously, we have reported electrophysiological, neurochemical and behavioral evidence for interactions between the 5-hydroxytryptamine$_{2A}$ (5-HT_{2A}) and mGlu2/3 receptors in the mPFC. The present studies were designed to investigate the effects in rats of adenosine A_1 receptor activation/blockade on a behavior modulated by 5-HT_{2A} receptor activation/blockade in the mPFC: head shakes induced in the rat by phenethylamine hallucinogens. An adenosine A_1 receptor agonist, N^6-cyclohexyladenosine (CHA) suppressed head shakes induced by activation of 5-HT_{2A} receptors with the phenethylamine hallucinogen (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride (DOI). An adenosine A1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), enhanced DOI-induced head shakes and blocked the suppressant action of an adenosine A_1 receptor agonist on DOI-induced head shakes. Thus, the pattern of activity for an agonist and antagonist at the adenosine A1 receptor with respect to modulating DOI-induced head shakes is similar to the pattern observed with mGlu2/3 receptor agonists and antagonists. These novel observations with an adenosine A_1 receptor agonist suggests that this pharmacological action could contribute to antipsychotic effects in addition to thymoleptic effects.

Keywords

head shakes; phenethylamine hallucinogens; DOI; adenosine; glutamate; medial prefrontal cortex

1. Introduction

Activation of metabotropic glutamate2/3 (mGlu2/3) receptors by orthosteric agonists recently has been shown to be an effective therapeutic approach for neuropsychiatric illness with suspected divergent etiology and pathophysiology such as generalized anxiety disorder and schizophrenia (Dunayevich et al., 2008; Patil et al., 2007). Blockade of neurotransmitter release, especially glutamate, via activation of mGlu2 autoreceptors is a prominent role played by mGlu2/3 receptor agonists (Cartmell et al., 2000b; Schoepp, 2001). Activation of mGlu2

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receptors within the medial prefrontal cortex (mPFC) may decrease glutamate release induced by activation of cortical 5-HT_{2A} receptors or the disinhibitory effects of NMDA receptor antagonists on local circuit interneurons in the hippocampus or mPFC (Jodo et al., 2004; Homayoun and Moghaddam, 2007). Thus, activation of mGlu2 autoreceptors appears to attenuate the electrophysiological, neurochemical and behavior effects of 5-HT_{2A} receptor activation or NMDA receptor blockade (Benneyworth et al., 2007; Carli et al., 2004; Cartmell et al., 2000a; Galici et al., 2005; Gewirtz and Marek, 2000; Higgins et al., 2003; Homayoun et al., 2005; Marek et al., 2000; Moghaddam and Adams, 1998; Muschamp et al., 2004).

Activation of adenosine A_1 receptors, like mGlu2 receptors, is known to decrease glutamate release in many limbic-related brain regions, as measured by electrophysiological recordings from layer V pyramidal cells of the medial prefrontal cortex (Brand et al., 2001; Marek et al., 2000; Stutzman et al., 2001). Previous preclinical *in vivo* testing with adenosine A_1 receptor agonists has supported potential anxiolytic (Florio et al., 1998; Jain et al., 1995) and antipsychotic (Andine et al., 1999; Browne and Welch, 1982; Florio et al., 1998; Gotoh et al., 2002; Jain et al., 1995; Sills et al., 1999) action.

Therefore, the present studies were designed to investigate the effects of adenosine A_1 receptor activation/blockade with respect to a behavior which may be mediated and/or modulated by increased glutamate release in the mPFC. Since head shakes induced by phenethylamine hallucinogens such as (1-(2,5,dimethoxy-4-iodophenyl))-2-aminopropane (DOI) appear to be mediated by activation of 5-HT_{2A} receptors in the mPFC and are also suppressed by activation of mGlu2 autoreceptors, these DOI-induced head shakes were chosen as the first *in vivo* model system to test in the rat (Benneyworth et al., 2007; Gewirtz and Marek, 2000; Gonzalez-Maeso et al., 2007; Klodzinska et al., 2002; Willins and Meltzer, 1997). Another justification supporting DOI-induced head shakes as a model system is that *in vivo* microdialysis studies have suggested that systemic administration of phenethylamine hallucinogenic drugs is associated with increased extracellular glutamate in the mPFC and somatosensory cortex (Muschamp et al., 2004; Scruggs et al., 2003). Consistent with these studies in rodents, administration of phenethylamine hallucinogens have also been demonstrated to increase regional cerebral blood flow in the mPFC and other neocortical areas in healthy human volunteers (Vollenweider et al., 1997).

Therefore, in this study, we examined the effects of the adenosine A_1 receptor agonist N^6-cyclohexyladenosine (CHA) on DOI-induced head shakes to examine a behavior induced by activation of 5-HT_{2A} receptors in the rat prefrontal cortex. The suppressant action of CHA on DOI-induced head shakes was tested for pharmacological specificity using the adenosine A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX or PD116,948). The pharmacology of adenosine A_1 receptor ligands (Bruns et al., 1987; Salvatore et al., 1993) with respect to DOI-induced head shakes is consistent with previous preclinical predictions that adenosine A1 agonists might demonstrate antipsychotic action.

2. Materials and Methods

2.1. Subjects

Male Sprague-Dawley rats (n=102) weighing between 150–300 g at the initial behavioral testing were used (Harlan, Indianapolis, IN). They were housed in suspended stainless wire cages(18 × 36 × 20 cm) with two to four rats occupying each cage. The colony room was maintained at 20 °C and relative humidity (60%). The room was illuminated 12 hr/day (07:00–19:00). All rats had free access to laboratory chow (Teklad 4% Rat Diet) and water except during experimental sessions. All animals were treated in accord with the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. In addition, all protocols were approved by the Yale University Animal Care and Use Committee.

2.2. Behavioral observations

All experiments were performed between 9:00 and 16:00. The animals were transferred to a clear polycarbonate cage (43×21.5×20 cm) with a sawdust-covered floor. All the rats were habituated to the testing environment with a saline injection at least several days prior to the first DOI/vehicle, CHA/vehicle or DPCPX/vehicle injection. The animals were observed during consecutive 5 min periods for a total of 30 min following the DOI injection. In addition to counting each head shake response, forward locomotion (movement from one end to the other end of the cage was scored as one cross), and rearing (raising up on hind limbs) was also recorded.

2.3. Statistical analysis

A one-factor or two-factor ANOVA was carried out for measurement of head shake, rearing and horizontal locomotor activity. The Dunnett test or Neuman-Keuls test was used for the one-factor or two-factor ANOVAs, respectively. The effect of the adenosine A_1 receptor agonist CHA was assessed using a between-subject design where a different group of rats were used for each dose (n=8). The effect of the adenosine A_1 receptor antagonist DPCPX/vehicle with DOI/vehicle was tested using a with-in subject design (n=10) and a repeated measures ANOVA. The interaction of the adenosine A_1 receptor antagonist DPCPX and the adenosine A_1 receptor agonist CHA with respect to behavior induced by DOI was assessed using a between-subject design (n=10). The level of significance was set for $p<0.05$.

2.4. Drugs

Doses were calculated on the basis of the salt forms. The drugs were dissolved in saline, neutralized to a pH ~ 7.4, and injected IP in a volume of 1 ml/kg body weight. The adenosine A_1 receptor agonist CHA (N^6-cyclohexyladenosine) and the adenosine A_1 receptor antagonist DPCPX (8-cyclopentyl-1,3-dimethylxanthine) were purchased from Sigma-Aldrich (St. Louis, MO) and Tocris (Ballwin, MO), respectively. The 5-$HT_{2A/2B/2C}$ receptor partial agonist DOI, (±)-2,5-dimethoxy-4-iodoamphetamine hydrochloride, was purchased from Research Biochemicals International (Natick, MA). At least a two week interval occurred between successive DOI injections to minimize tachyphylaxis of the DOI-induced head shakes. A dose of DOI (1.25 mg/kg, ip) producing a near-maximum of head shakes over a 30 min period was chosen for experiments testing suppression of head shakes by CHA (Gewirtz and Marek, 2000). DOI-induced head shakes increase in a monotonic dose-dependent manner through 9 mg/kg using Sprague-Dawley rats (Pranzatelli, 1990). DPCPX/vehicle, CHA/vehicle and DOI/vehicle were administered 30, 15 and 0 min, respectively, prior to beginning the 30 min observation period.

3. Results

3.1. The adenosine A_1 receptor agonist CHA suppresses DOI-induced head shakes

The adenosine A_1 receptor agonist CHA (31.3–125 μg/kg, i.p.) suppressed DOI-induced head shakes in a dose-dependent manner ($F(3,28)=4.44$, $p<0.05$; Fig. 1). The 62.5 and the 125 μg/kg CHA dose conditions combined with DOI were significantly different from DOI (1.25 mg/kg) alone ($p<0.05$ and $p<0.01$, respectively, Newman-Keuls test). CHA (31.3–125 μg/kg, i.p.) also suppressed the frequency of rearing enhanced by DOI in a dose-dependent manner ($F(3,28)=11.32$, $p<0.001$; Fig. 1). The frequency of rearing was significantly decreased when rats were treated with each dose condition ($p<0.01$, Newman-Keuls test). A trend for CHA in reducing locomotion in DOI-treated rats was also found ($F(3,28)=2.81$, $p=0.058$, not shown). DOI tended to double locomotor activity, although only a trend was found when comparing DOI (1.25 mg/kg) vs vehicle ($t(7)=2.095$, $p=0.074$, not shown).

No spontaneous head shakes were observed in these rats over the 30 min observation periods used in the absence of DOI. However, CHA (31.3–125 μg/kg) did suppress basal levels of rearing behavior ($F(3,28)=3.33$, $p<0.05$; Fig. 1), with significant effects only at the 31.3 and 62.5 μg/kg dose levels ($p<0.05$ and $p<0.01$, respectively). CHA did not alter the basal horizontal locomotor activity ($F(3,28)=1.75$, $p>0.1$, not shown).

3.2. The adenosine A_1 receptor antagonist DPCPX enhances DOI-induced head shakes

The adenosine A_1 receptor antagonist DPCPX (10 mg/kg, i.p.) enhanced head shakes induced by a lower DOI dose (0.625 mg/kg, i.p.; Fig. 2) than the first experiment. A significant effect was observed for DPCPX ($F(1,9)=6.93$, $p<0.05$), DOI ($F(1,9)=105.0$, $p<0.001$), and the interaction between DPCPX and DOI ($F(1,9)=6.93$, $p<0.05$). DPCPX nearly doubled the frequency of DOI-induced head shakes ($p<0.01$, Newman-Keuls test). In contrast to this significant interaction, neither the adenosine A_1 receptor antagonist factor nor the interaction factor between the A_1 receptor antagonist and DOI were significant for either rearing behavior or forward locomotion (not shown).

3.3. DPCPX reverses the suppressant action of CHA on DOI-induced head shakes

The adenosine A_1 receptor antagonist DPCPX (1.25–20 mg/kg, i.p.) blocked the suppressant action of CHA (62.5 μg/kg, i.p.) on DOI(1.25 mg/kg, i.p.)-induced head shakes in a dose-dependent manner ($F(5,53)=10.09$, $p<0.001$, Fig. 3). CHA suppressed DOI-induced head shakes by 83% ($p<0.001$, Newman-Keuls test) while each DPCPX dose significantly reversed the suppressant action of CHA on DOI-induced head shakes ($p<0.05$ for the 1.25 and 5 mg/kg dose, $p<0.01$ for the 10 mg/kg dose, and $p<0.001$ for the 20 mg/kg dose). While CHA suppressed rearing that was increased by DOI, a dose-dependent reversal by DPCPX was not observed.

4. Discussion

This is the first known demonstration that activation of adenosine A_1 receptors, potentially by suppressing glutamate release in the prefrontal cortex and associated limbic regions, blocks the behavioral effect of a serotonergic hallucinogen used as a preclinical psychosis screen. The demonstration that acute administration of phenethylamine hallucinogens and other 5-HT_{2A} receptor agonists into the prelimbic region of the rodent medial prefrontal cortex induces head shakes (Willins and Meltzer, 1997) is particularly important for a number of reasons. First, the DOI-induced head shake response is suppressed or enhanced by drugs which decrease or increase glutamate release, respectively, by acting on mGlu2 receptor autoreceptors (Benneyworth et al., 2007; Gewirtz and Marek, 2000; Klodzinska et al., 2002). Second, two different selective 5-HT_{2A} receptor antagonists were found to possess modest antipsychotic effects in large multi-centered studies intermediate between placebo and haloperidol (Marder, 1999; Meltzer et al., 2004). This raises the possibility that the prefrontal cortex may be an important component of the circuitry mediating the antipsychotic responses observed with the mGlu2/3 receptor agonist prodrug LY2140023 and the 5-HT_{2A} receptor antagonists. In addition to mGlu2/3 receptor agonists and adenosine A1 receptor agonists both suppressing DOI-induced head shakes, activation of both adenosine A_1 receptors and mGlu2 receptors is known to suppress excitatory synaptic currents induced by 5-HT_{2A} receptor activation in the rat or mouse medial prefrontal cortex using slice preparations (Benneyworth et al., 2007; Klodzinska et al., 2002; Marek et al., 2000; Stutzman et al., 2001; Zhai et al., 2003).

These results extend previous preclinical *in vivo* research suggesting antipsychotic properties for adenosine A_1 receptor agonists (Andine et al., 1999; Browne and Welch, 1982; Florio et al., 1998; Gotoh et al., 2002; Jain et al., 1995; Sills et al., 1999). Serotonergic hallucinogens as a pharmacological model for psychosis actually predated the use of non-competitive NMDA

receptor antagonists or amphetamine/methamphetamine (Shaw and Woolley, 1956; Woolley and Shaw, 1954). Head shakes/head twitches induced by activation of 5-HT_{2A} receptors in rodents has been one of the most commonly used preclinical behavioral models to back translate the psychotomimetic effects of LSD, mescaline and psilocybin analogues. Adenosine A_1 receptor agonists, like mGlu2/3 receptor agonists are capable of suppressing the presumed psychotomimetic effects in rodents of all three major classes of challenge agents, non-competitive NMDA receptor antagonists, amphetamine and serotonergic hallucinogens (Heffner et al., 1989; Andine et al., 1999; Gewirtz and Marek, 2000; Rorick-Kehn et al., 2007). This sharing of psychopharmacological effects between adenosine A1 receptor agonists and mGlu2/3 receptor agonists is especially poignant given the clinical observations that a prodrug for a mGlu2/3 receptor agonist improved both the positive and negative symptoms of schizophrenia in a double-blind, placebo-controlled study (Patil et al., 2007).

Involvement of prefrontal cortical 5-HT_{2A} receptors in these effects is supported by previous studies demonstrating that (1) activation of 5-HT_{2A} receptors in the rat PFC alone is sufficient to induce head shakes and (2) a rescue of forebrain (prefrontal cortex, neocortex and claustrum) 5-HT_{2A} receptors is sufficient to support hallucinogen-induced head twitches in a mouse strain where hallucinogen-induced head twitches had been lost following constitutive disruption of 5-HT_{2A} receptors (Gonzalez-Maeso et al., 2007; Willins and Meltzer, 1997). Furthermore, both electrophysiological and in vivo dialysis experiments have suggested that activation of mGlu2 receptors within the mPFC suppresses glutamate release induced by 5-HT_{2A} receptor activation (Benneyworth et al., 2007; Marek et al., 2001; Marek et al., 2000; Muschamp et al., 2004).

At a more fundamental level, the constellation of shared electrophysiological, biochemical and behavioral effects between adenosine A_1 receptor agonists and mGlu2/3 receptor agonists or mGlu2 potentiators emphasizes similar biological roles played by mGlu2 heteroceptors and adenosine A_1 heteroceptors (Fredholm and Dunwiddie, 1988; Goodman et al., 1983; Schoepp, 2001). For example, activation of mGlu2 receptors and adenosine A_1 receptors suppresses glutamate release from thalamocortical pathways (Fontanez and Porter, 2006; Marek et al., 2001). The plethora of behavioral effects predicting antipsychotic action for the activation of adenosine A_1 heteroceptors and mGlu2 receptors may also involve a wider limbic-related distribution of these receptors where they may play similar roles.

Electrophysiological studies in the mPFC are consistent with the hypothesis that adenosine A_1 receptors suppress glutamate release induced by 5-HT_{2A} receptors in a fashion similar to mGlu2 receptor activation. Given (1) the similarity between the effects of mGlu2 receptor activation and adenosine A_1 receptor activation in the PFC; (2) the similar laminar distribution of rodent 5-HT_{2A} receptors, mGlu2 receptors and adenosine A_1 receptors (Fastbom et al., 1987; Lopez-Gimenez et al., 1997; Marek et al., 2001; Marek et al., 2008; Marek et al., 2000), and (3) the suggestion that 5-HT_{2A} and mGlu2 receptors interact via a molecular complex (Gonzalez-Maeso et al., 2008), then the presence or absence of a molecular complex between 5-HT_{2A} and adenosine A_1 receptors may be important for evaluating this new theory postulated to explain physiological interactions between 5-HT_{2A} and mGlu2 receptors of relevance for psychosis and antipsychotic drug effects. Conversely, activation of a number of G_q-linked GPCRs acts similar to 5-HT_{2A} receptors at inducing spontaneous 5-HT-induced EPSCs (e.g., α_1-adrenergic, orexin-2, neurokinin-3, and mGlu5 receptors). These G_q-linked GPCRs might be expected to similarly interact with glutamatergic autoreceptors (mGlu2, mGlu4, mGlu8) and class A GPCR heteroceptors (adenosine A_1 heteroceptors and u-opioid heteroceptors) similar to the proposed interaction of 5-HT_{2A} and mGlu2 receptors. It is also conceivable that the effects of adenosine A_1 receptor agonists might be directly acting on other receptor that also oppose the effects of 5-HT_{2A} receptors such as 5-HT_{1A} receptors (Zgombick et al., 1989). However, this type of relationship would not appear as parsimonious as the

alternative hypothesis that a number of Gi/Go-coupled GPCRs similarly oppose the effects of 5-HT_{2A} receptor activation by virtue of sharing aspects of post-receptor transduction pathways.

Other brain regions may mediate the effects of systemic administration of adenosine A_1 receptor agonists and antagonists on DOI-induced head shakes. Adenosine A_1 receptor activation may suppress neurotransmitter release in a number of regions associated with neuropsychiatric illness ranging from the PFC, hippocampus, the striatum, thalamus, and brainstem nuclei associated with attention and arousal via a number of mechanisms (Fredholm and Dunwiddie, 1988; Ochiishi et al., 1999; Rivkees et al., 1995). The distribution of mGlu2 receptor mRNA and protein in limbic-related regions is similar to the pattern observed for adenosine A_1 receptor mRNA and protein.

The present results may be relevant to understanding additional domains of behavior which might be impacted by modulation of adenosine A_1 receptors. Previously, drugs which block adenosine A_1 receptors such as caffeine and PD 116,600 have been found to impair performance of rats on a differential-reinforcement-of-low rate (DRL) 72-s operant schedule consistent with an enhancement of impulsivity (Marek et al., 1993). Activation of 5-HT_{2A} receptors has been found to increase motoric impulsivity while blockade of 5-HT_{2A} receptors appears to enhance the ability of animals to wait before making a response when performing on DRL 72-s schedules (Ardayfio et al., 2008; Carli et al., 2004; Winstanley et al., 2004). Given the growing literature supporting these findings, determining the effects of adenosine A_1 receptor agonists and mGlu2 receptor potentiators or mGlu2/3 receptor agonists in tasks assessing dysfunction of the prefrontal cortex is of great heuristic and potential therapeutic interest.

5. Conclusions

The present study provides a third psychotomimetic animal model predicting antipsychotic action for adenosine A_1 receptor agonists. Adenosine A_1 receptor agonists have a primary role in suppressing glutamate release from heteroceptors from axons throughout the forebrain, including the prefrontal cortex . These results are consistent with the hypothesis that drugs which suppress glutamate release from dysfunctional limbic circuits, such as mGlu2 receptor agonists or potentiators, will be useful antipsychotic drugs.

Acknowledgements

These experiments were performed in the Department of Psychiatry at the Yale University School of Medicine and the Ribicoff Research Facilities of the Connecticut Mental Health Center. Support from the National Institutes of Health Grants RO1 MH62186 and K08 MH01551 and the state of Connecticut is gratefully acknowledged. I also thank Allyson Abo, Sara Heron, Angela Keene, and Kim Reiss for technical assistance.

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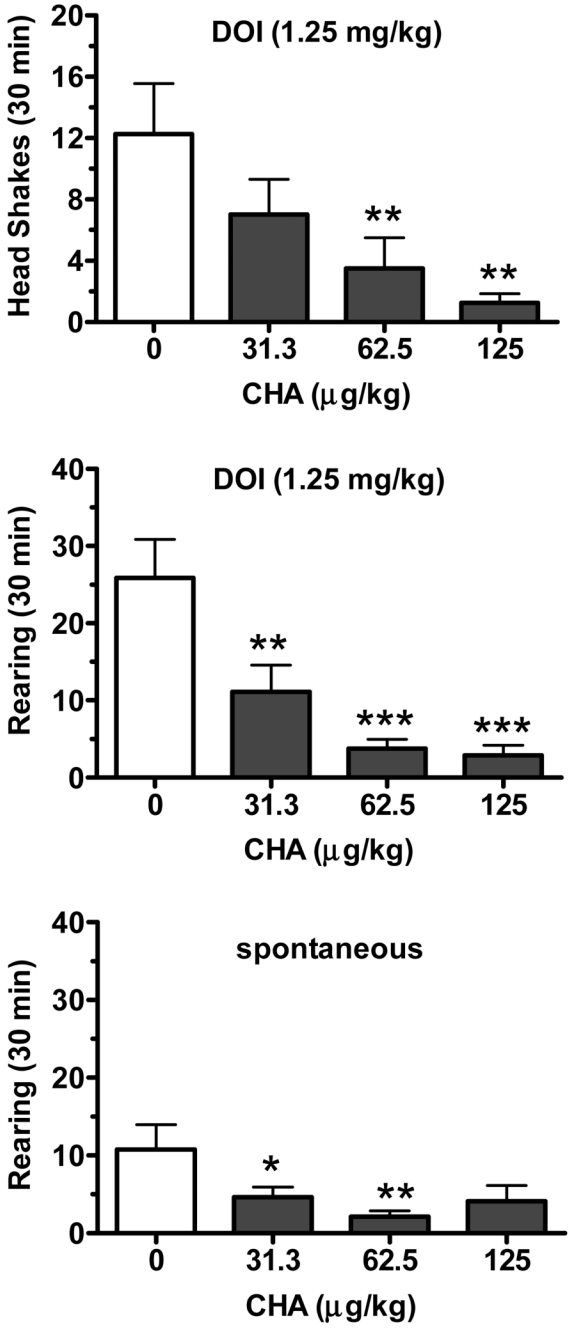

Fig. 1.

Dose-dependent suppression of DOI-induced head shakes and rearing by the adenosine A_1 receptor agonist CHA (31.3–125 μg/kg, i.p.). The top panel displays the frequency of DOI (1.25 mg/kg, i.p.)-induced head shakes (mean ± SEM) 30 min following treatment with either vehicle or CHA (31.3, 62.5, 125 μg/kg; n=8/condition). In the absence of DOI, no head shakes were counted in rats similarly treated with vehicle or CHA (not shown) and observed for a 30 min period. The middle and lower panels display the frequency of rearing for the same rats under the same treatment conditions, except in the lower panel where DOI was not injected. * $p<0.05$; ** $p<0.01$; *** $p<0.001$ compared to the DOI/vehicle condition.

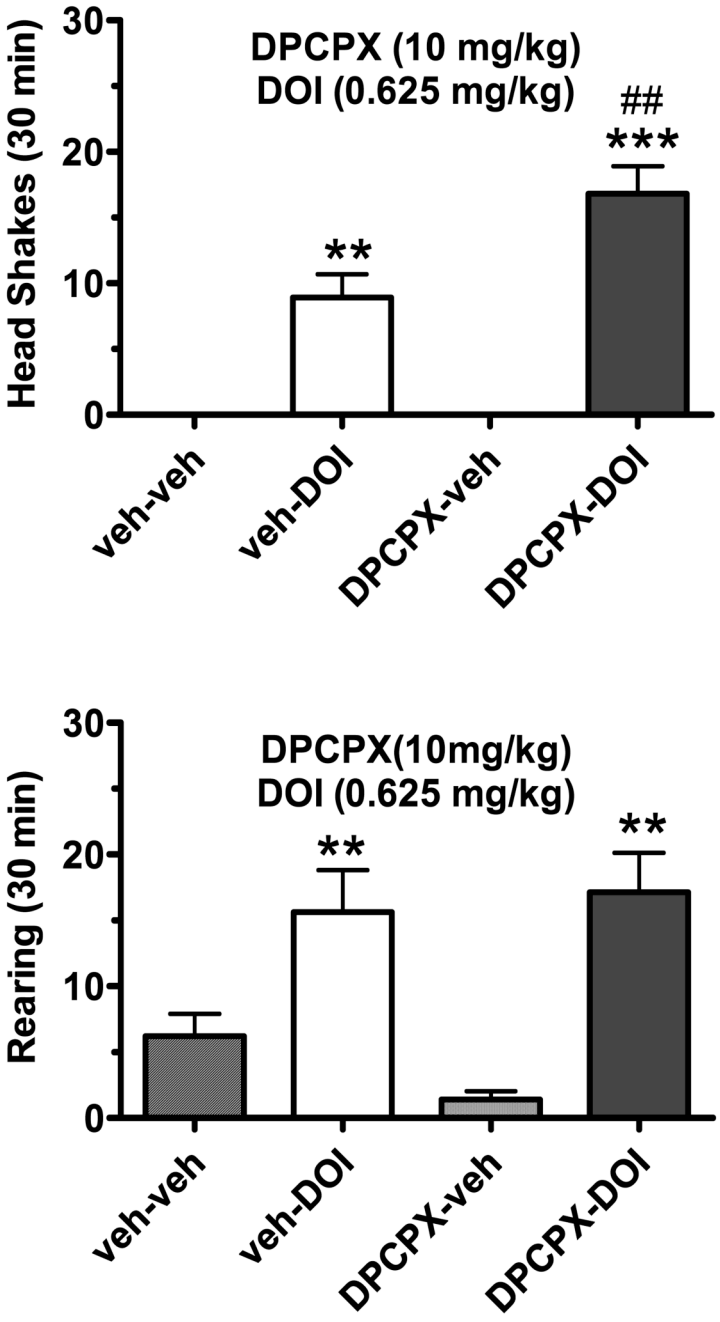

Fig. 2.

The adenosine A_1 receptor antagonist DCPCX enhances DOI-induced head shakes. The top panel displays the frequency of DOI (1.25 mg/kg, i.p.)-induced head shakes (mean ± SEM) in the presence and absence of the DCPCX (10 mg/kg, i.p.; n=10). The bottom shows the absence of an effect of this DCPCX dose on rearing associated with DOI.

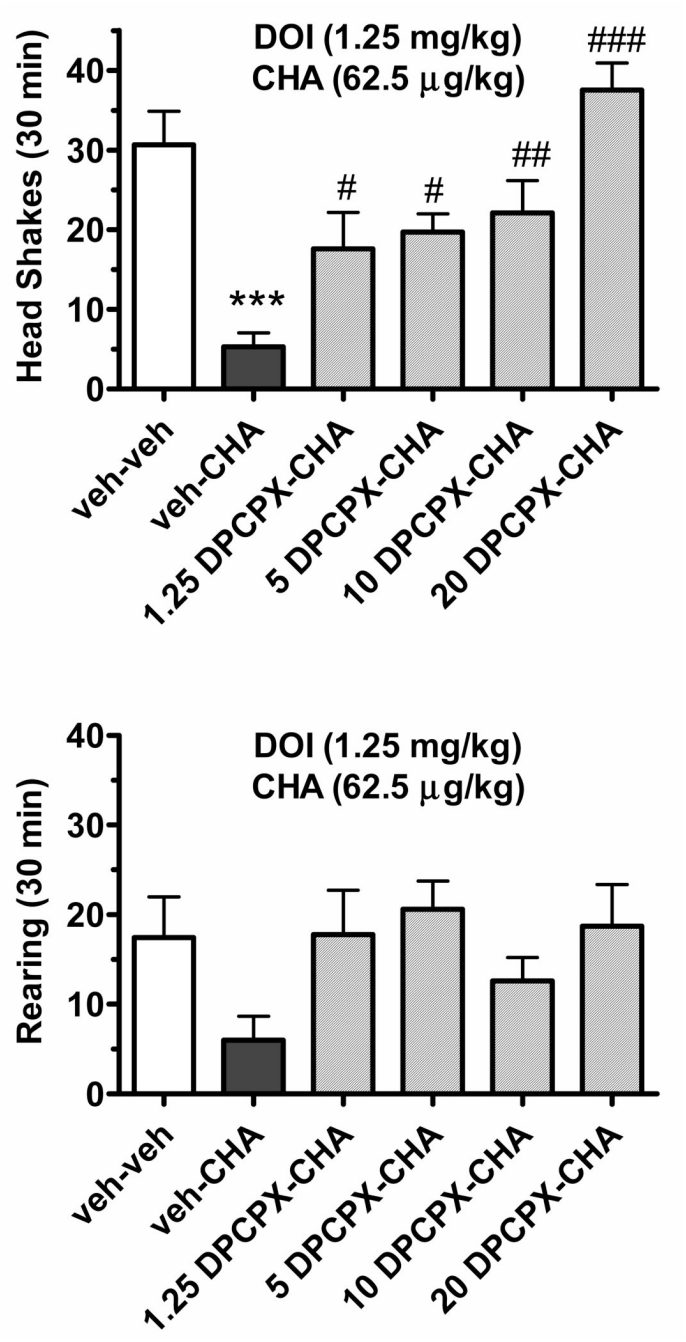

Fig. 3.

Dose-dependent attenuation by the adenosine A_1 receptor antagonist DCPCX of the suppressant action of the adenosine A_1 agonist CHA on DOI-induced head shakes. The top panel shows the frequency of DOI (1.25 mg/kg, ip)-induced head shakes in rats also treated with vehicle or CHA (62.5 µg/kg, i.p.) and either vehicle or DCPCX (1.25–20 mg/kg; n=10/condition). The bottom panel shows the frequency of rearing under similar treatment conditions where again, all rats received DOI treatment immediately prior to the observation period. * $p<0.05$, compared to the vehicle-vehicle condition; # $p<0.05$, ## $p<0.01$, ### $p<0.001$ compared to the CHA-vehicle condition, respectively.