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Original article

Evaluation of antidepressant-like and anxiolytic-like activity of purinedione-derivatives with affinity for adenosine A_{2A} receptors in mice

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ABSTRACT

Background: It has recently been suggested that the adenosine A_{2A} receptor plays a role in several animal models of depression. Additionally, A_{2A} antagonists have reversed behavioral deficits and exhibited a profile similar to classical antidepressants.
Methods: In the present study, imidazo- and pyrimido[2,1-f]purinedione derivatives (KD 66, KD 167, KD 206) with affinity to A_{2A} receptors but poor A_1 affinity were evaluated for their antidepressant- and anxiolytic-like activity. The activity of these derivatives was tested using a tail suspension and forced swim test, two widely-used behavioral paradigms for the evaluation of antidepressant-like activity. In turn, the anxiolytic activity was evaluated using the four-plate test.
Results: The results showed the antidepressant-like activity of pyrimido- and imidazopurinedione derivatives (*i.e.* KD 66, KD 167 and KD 206) in acute and chronic behavioral tests in mice. KD 66 revealed an anxiolytic-like effect, while KD 167 increased anxiety behaviors. KD 206 had no effect on anxiety. Furthermore, none of the tested compounds increased locomotor activity.
Conclusion: Available data support the proposition that the examined compounds with adenosine A_{2A} receptor affinity may be an interesting target for the development of antidepressant and/or anxiolytic agents.

Introduction

In recent years, much attention has been paid to the role of adenosine A_{2A} receptors in Parkinson's disease (PD) and comorbid depression and anxiety. A_{2A} receptors mediate excitatory actions on the nervous system by coupling with Gs proteins, which stimulate adenylyl cyclase [1].These frequently occur in the central nervous system, where they are localized on neurons [2] and glial cells [3]. In the brain, they are concentrated in the basal ganglia especially in areas with dopaminergic nigrostriatal and mesolimbic pathways [4]. Within the striatum, A_{2A} receptors are localized on GABA-ergic striatopallidal neurons, where they are colocalized with dopamine D_2 receptors. They are located presynaptically and control the release of a variety of neurotransmitters [2]. Sarges et al. [5] suggested that A_2 selective non-xanthine adenosine antagonists induce activity in the swim test by a prolongation of escape-directed behavior, rather than by a locomotor stimulant effect. The A_{2A} receptor knockout mice showed increased mobility in forced swim and tail suspension tests [6,7]. There is considerable evidence that adenosine A_{2A} receptors are involved not only in behavioral despair [6–8], but also in learned helplessness [14], and cytokine- and reserpine-induced depression models [10,11]. In these models, adenosine A_{2A} antagonists reverse behavioral deficits and exhibit a profile similar to that of tricyclic antidepressants (TCAs). Moreover, adenosine A_{2A} receptor antagonists reverse reserpine- and haloperidol-induced motor deficits in animals [12]. It has been suggested that istradefylline (KW-6002, adenosine A_{2A} antagonist) may have beneficial effects on depression as well as on motor symptoms in patients with PD [13,14]. Furthermore, similarly to desipramine,

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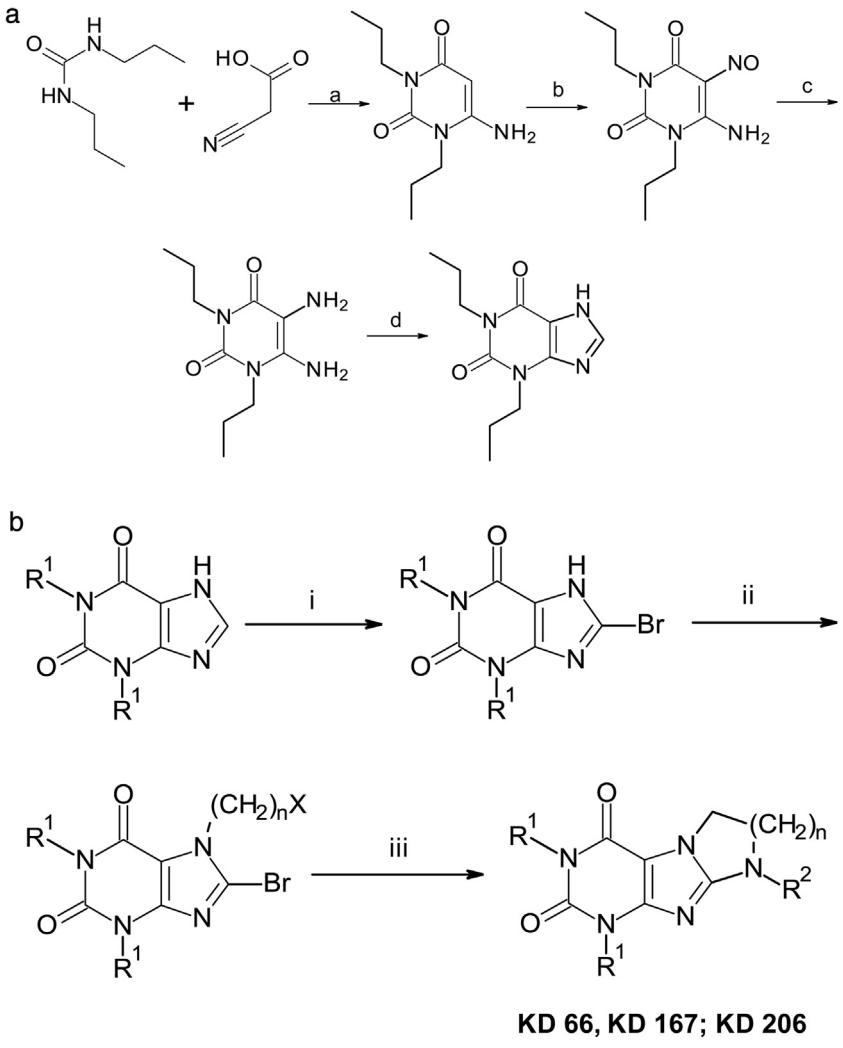
long-term caffeine (non-selective A_1/A_{2A} adenosine antagonist) exposure exerts an antidepressant effect in chronic unpredictable stress (CUS) [15]. Moreover, long treatment with A_{2A} antagonists reversed the mood and synaptic dysfunction caused by CUS [15]. Some antidepressants may have different impacts on anxiety. For instance, imipramine (IMI) is devoid of effects on anxiety, and, venlafaxine, and citalopram additionally have anxiolytic action. However, drugs such as desipramine, or maprotiline show anxiogenic effects [16,17]. Clinical pharmacological studies and models of genetically modified rodents have implicated caffeine in the modulation of different types of anxiety [18–20]. Given the antidepressant effect of purinedione-derivatives, we have attempted to determine their impact on anxiety.

The synthesis and pharmacological properties of some derivatives of purinediones have been described [21–23,27–29]. In the present paper, we report the results from pharmacological research on the activity of N-substituted 1,3- dimethyl- or 1,3-dipropyl- tetrahydropyrimido[1,2-*a*] purinediones and 1,3- dimethyl- dihydroimidazo-[1,2-*a*]-purine-dione (Fig. 1). We investigated the effect of these new compounds on depression- and anxiolytic-like behavior, using selected animal test. Also, the effect of compounds on spontaneous locomotor activity was studied in order to exclude false-positive results in the assessment of antidepressant and anxiolytic-like activity.

Materials and methods

Animals

The experiments were carried out on male Swiss Albino mice (CD-1) weighing 18–25 g. The animals were housed in groups of 15 in plastic cages (60 cm × 38 cm × 20 cm) with free access to water



KD 66: R^1- methyl; R^2- cyclohexyl; n- 2;
KD 167: R^1- propyl; R^2- 2-naphthyl; n- 2;
KD 206: R^1- methyl; R^2- cyclooctyl; n- 1;

Fig. 1. Chemical structures and syntheses of the test compounds: KD 66, KD 167, KD 206. (a) Synthesis of dipropylxanthine. a – $(CH_3CO)_2O$, CH_3COOH; b – $NaNO_2$, 50% CH_3COOH; c – $Na_2S_2O_4$, NH_3 aq; d – 40% HCOOH, NaOH aq. (b) Synthesis of imidazo- or pyrimido-[2,1-f]purinedione derivatives. i – 40% HBr, $NaClO_3$,AcOH; ii – $X(CH_2)_nX$, TEBA, K_2CO_3; iii – R^2-NH_2; X – Cl, Br; n – 2, 3.