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Guanosine may increase absence epileptic activity by means of A2A adenosine receptors in Wistar Albino Glaxo Rijswijk rats

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ABSTRACT

The non-adenosine nucleoside guanosine (Guo) was demonstrated to decrease quinolinic acid(QA)-induced seizures, spontaneously emerged absence epileptic seizures and lipopolysaccharide(LPS)-evoked induction of absence epileptic seizures suggesting its antiepileptic potential. It was also described previously that intraperitoneal (i.p.) injection of 20 and 50 mg/kg Guo decreased the number of spike-wave discharges (SWDs) in a well investigated model of human absence epilepsy, the Wistar Albino Glaxo Rijswijk (WAG/Rij) rats during 4th (20 mg/kg Guo) and 3rd as well as 4th (50 mg/kg Guo) measuring hours. Guanosine can potentially decrease SWD number by means of its putative receptors but absence epileptic activity changing effects of Guo by means of increased extracellular adenosine (Ado) cannot be excluded. An increase in the dose of i.p. injected Guo is limited by its low solubility in saline, therefore, we addressed in the present study whether higher doses of Guo, diluted in sodium hydroxide (NaOH) solution, have more potent antiepileptic effect in WAG/Rij rats. We confirmed that i.p. 50 mg/kg Guo decreased but, surprisingly, i.p. 100 mg/kg Guo enhanced the number of SWDs in WAG/Rij rats. Combined i.p. injection of a non-selective Ado receptor antagonist theophylline (5 mg/kg) or a selective Ado A_{2A} receptor ($A_{2A}R$) antagonist SCH 58261 (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine) (1 mg/kg) and a cyclooxygenase 1 and 2/COX-1 and COX-2 inhibitor indomethacin (10 mg/kg) with 100 mg/kg Guo decreased the SWD number compared to i.p. 100 mg/kg Guo alone. The results suggest that i.p. 100 mg/kg Guo can increase SWD number by means of the adenosinergic system.

Abbreviations: A_1R, adenosine A_1 receptor; $A_{2A}R$, adenosine A_{2A} receptor; Ado, adenosine; ADP, Ado diphosphate; AMP, Ado monophosphate; ATPA, do triphosphate; CNS, central nervous system; COX, cyclooxygenase; DMSO, dimethyl sulfoxide; EEG, electroencephalogram; FFT, Fast Fourier Transform; GABA, gamma-aminobutyric acid; GDP, Guo diphosphate; GMP, Guo monophosphate; Gn, guanine; GTP, Guo triphosphate; Guo, guanosine; IL-1β, interleukin-1β; IMP, Ino monophosphate; Ino, inosine; i.p., intraperitoneal; LPS, lipopolysaccharide; NaOH, sodium hydroxide; PGE_2, prostaglandin E_2; PTC day, post-treatment control experiment/day; QA, quinolinic acid; REM sleep, rapid eye movement sleep; SCH 58261, (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine; S.E.M., standard error of the mean; SWD, spike-wave discharge; SWS, slow wave sleep; WAG/Rij, Wistar Albino Glaxo/Rijswijk.

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1. Introduction

Region-dependent functions of non-adenosine nucleoside guanosine (Guo) have been suggested in the brain (Kovács et al., 2010, 2011c; Kovács and Dobolyi, 2013). Guanosine has trophic effects on neurons (Rathbone et al., 1999), stimulates astrocyte proliferation (Ciccarelli et al., 2000) and protects glial cells against 6-hydroxydopamine toxicity (Giuliani et al., 2015). Moreover, Guo modulates the glutamatergic system by the increase of glutamate uptake, which results in a decrease in glutamate-induced excitability (Frizzo et al., 2003; Schmidt et al., 2007). It was described previously that Guo (up to intraperitoneal/i.p. 240 mg/kg) is well tolerated with no obvious central nervous system (CNS) side effects and renal or hepatic impairments (Schmidt et al., 2010a, 2010b). Consequently, Guo and its analogs may have therapeutic effect in CNS diseases, such as neurodegenerative diseases, cerebral ischemia and seizures (Deutsch et al., 2008; Giuliani et al., 2015; Kovács and Dobolyi, 2013; Schmidt et al., 2007). Indeed, it has also been demonstrated that Guo decreased quinolinic acid(QA)-induced seizures (Schmidt et al., 2000; Soares et al., 2004) and attenuated both spontaneously emerged absence epileptic activity and lipopolysaccharide(LPS)-evoked increase in number of spike-wave discharges (SWDs) in Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats (Kovács et al., 2015a,b) suggesting its antiepileptic potential (Kovács et al., 2015a; Kovács and Dobolyi, 2013; Schmidt et al., 2007).

As Guo may (i) be entered to the brain *via* the blood-brain barrier (Ipata and Pesi, 2016; Kovács et al., 2011c) and metabolized both

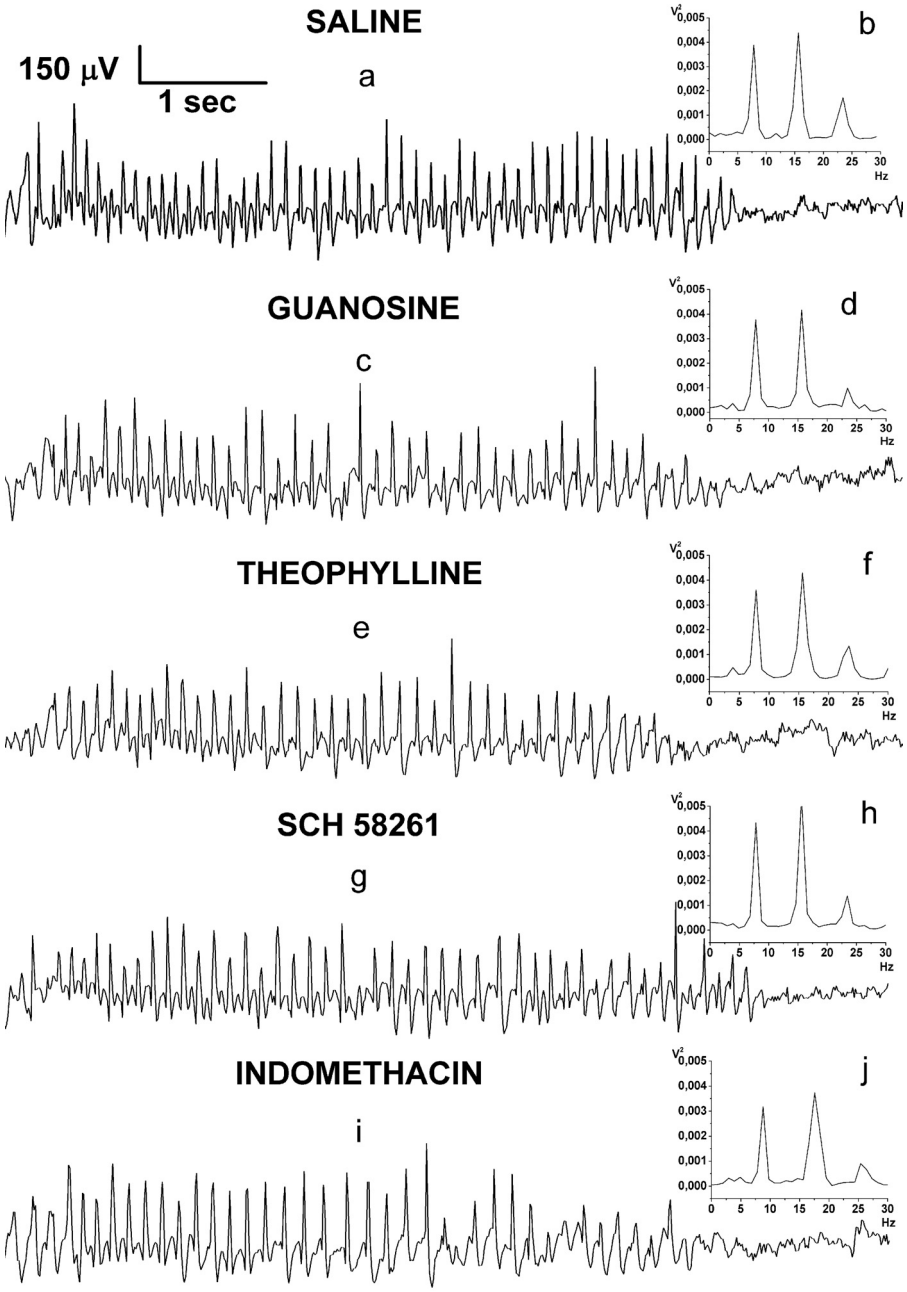

Fig. 1. SWDs and their frequency recorded from WAG/Rij rats after i.p. injection of saline (a and b), guanosine (100 mg/kg) (c and d), theophylline (5 mg/kg) (e and f), (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine (SCH 58261, 1 mg/kg) (g and h) and indomethacin (10 mg/kg) (i and j) alone between 60 – 90 min. Abbreviations: SCH 58261: (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine.