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Intracerebroventricular administration of inosine is anticonvulsant against quinolinic acid-induced seizures in mice: An effect independent of benzodiazepine and adenosine receptors

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ABSTRACT

Inosine (INO) has an anticonvulsant effect against seizures induced by antagonists of GABAergic system. Quinolinic acid (QA) is an agonist NMDA receptors implicated in the neurobiology of seizures. In the present study, we investigated the anticonvulsant effect of intracerebroventricular (i.c.v.) INO administration against QA-induced seizures in adult mice. We also investigated whether the benzodiazepines (BZ) or adenosine (ADO) receptors were involved in the INO effects. Animals were pretreated with an i.c.v. injection of either vehicle or INO before an i.c.v. administration of 4 μl QA (36.8 nmol). All animals pretreated with vehicle followed by QA presented seizures. INO protected against QA-induced seizures in a time and dose dependent manner (up to 60% at 400 nmol, 5 min before QA injection). Diazepam (DZ) and ADO (i.c.v.) also exhibited anticonvulsant effect against QA induced seizures. Additionally, i.p. administration of either flumazenil, a BZ receptor antagonist, or caffeine, an ADO receptor antagonist, did not change the anticonvulsant potency of INO i.c.v. injection, but completely abolished the DZ and ADO anticonvulsant effects, respectively. In conclusion, this study demonstrated that INO exert anticonvulsant effect against hyperactivity of the glutamatergic system independently of BZ or ADO receptors activation.

1. Introduction

The purinergic system including adenine, guanine and hypoxanthine, and their respectively nucleosides and nucleotides, has an important role in the modulation of central nervous system (CNS) activity (Abbracchio et al., 2009; Hasko et al., 2004; Schmidt et al., 2007; Schmidt and Souza, 2010). Several works have reported that the cerebral spinal fluid (CSF) levels of purine nucleosides (adenosine, guanosine and inosine) are augmented after a single seizure episode (Dunwiddie and Masino, 2001; Latini and Pedata, 2001; Lewin and Bleck, 1981; Oses et al., 2004; Winn et al., 1980). Most of these studies suggest that purine nucleosides have an important role in terminated seizures.

The potential anticonvulsant effect of inosine (INO) began to be investigated in the late 70's, and early 80's (Lewin and Bleck, 1985; Marangos et al., 1981a, 1981c; Skolnick et al., 1979). It was demonstrated that intracerebroventricular (i.c.v) (Skolnick et al., 1979) and subcutaneous (s.c.) (Lewin and Bleck, 1985) INO injection was able to increase the latency of pentylenetetrazol (PTZ)-induced seizure in mice. Additionally, the threshold for seizures induced by both, bicuculline and picrotoxin were significantly raised after INO s.c. administration (Lewin and Bleck, 1985). To note, PTZ, bicuculline and picrotoxin are inhibitors of the GABAergic complex receptor GABA-A, which contains binding sites for GABA, barbiturates, benzodiazepines (BZ), picrotoxin, and neurosteroids (McKernan and Whiting, 1996). GABA is recognized as the principal inhibitory neurotransmitter in the CNS and administration of GABA agonists is able to suppresse seizures (Treiman, 2001).

Several studies have proposed that INO exerts its anticonvulsant effects by acting on BZ binding sites in GABA-A receptors (BZ receptors). BZ are classical anticonvulsants, commonly used in the clinical practice, BZ increase the binding of GABA to GABA-A receptors, enhancing GABA-mediated inhibition (Treiman, 2001). INO competitively displaces the binding of diazepam (DZ – a classical BZ receptors ligand) to CNS cell membrane (Asano and Spector, 1979; MacDonald et al., 1979; Marangos et al., 1981b, 1981c).

Recent reports showed that INO can also bind and activate adenosine (ADO) receptors (Hasko et al., 2004). The anticonvulsant potential of ADO

Abbreviations: INO, inosine; QA, quinolinic acid; BZ, benzodiazepines; ADO, adenosine; DZ, diazepam; CNS, central nervous system; CSF, cerebral spinal fluid; i.c.v., intracerebroventricular; s.c., subcutaneous; i.p., intraperitoneal; PTZ, pentylenetetrazol; CAF, caffeine; FLU, flumazenil; PBS, phosphate buffer saline; NMDA, N-Methyl-D-aspartic acid; GABA, gamma-amino butyric acid.

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has been demonstrated previously (Avsar and Empson, 2004; Dragunow and Faull, 1988; Fedele et al., 2006; Fredholm et al., 2005; Tomé et al., 2010; Young and Dragunow, 1994). ADO acts on different receptors in the brain (A1, A2A, A2B and A3). INO activates A1 receptors that exhibited an anticonvulsant effect. However, to our knowledge, the hypothesis that the anticonvulsant effect of INO may involve adenosinergic system was never investigated.

Quinolinic acid (QA), an endogenous metabolite of tryptophan, may be involved in the pathogenesis of various CNS disorders including epilepsy (Heyes et al., 1990; Stone, 2001). QA is a well know NMDA agonist (Stone, 1993) and, stimulating synaptosomal glutamate release(Tavares et al., 2005), increasing glutamate uptake by synaptic vesicles (Tavares et al., 2008) and inhibiting glutamate uptake by astrocytes (Tavares et al., 2002), over stimulates the glutamatergic system. QA has been proposed to be a useful model of acute seizures in rodents (Schmidt et al., 2007; Schmidt and Souza, 2010).

The aim of the present study was to investigate the anticonvulsant potential of INO i.c.v. injection in a mouse model of acute seizures induced by QA. Attempts have been made to investigate some of the possible mechanisms underlying the anticonvulsant action of INO.

2. Materials and methods

2.1. Animals

Male adult Swiss albino mice (35–45 g) were kept on a 12 h light/dark cycle (light on at 7:00 AM) at temperature of 22 ± 1 °C, housed in plastic cages with tap water and commercial food *ad libitum*. All procedures were carried out according to the Brazilian Society for Neuroscience and Behavior's recommendations for animal care and the EC Directive 86/609/EEC for animal experiments, designed to minimize the suffering and the number of animals used. All behavioral procedures were conducted between 3:00 and 6:00 PM. Each animal was used only once.

2.2. Chemicals

Inosine (INO), adenosine (ADO), caffeine (CAF), flumazenil (FLU) and diazepam (DZ) were purchased from Sigma (St. Louis, MO, USA). The anesthetic sodium thiopental was obtained from Cristália (Itapira, SP, Brazil). All others chemicals of analytical grade were from standard suppliers. INO, ADO and CAF were dissolved in phosphate buffer saline (PBS, pH = 7.4) containing (in mM): Na_2HPO_4 7.7, NaH_2PO_4 2.7 and NaCl 154. DZ and FLU were dissolved in PBS plus 20% Tween 80 (PBS + Tween).

2.3. Surgical procedure

Surgery and i.c.v. infusion techniques were adapted from Schmidt et al., 2000 (Schmidt et al., 2000). Animals were anesthetized with sodium thiopental (60 mg/kg, 10 ml/kg, i.p.). In a stereotaxic apparatus, the skin of the skull was removed, and an i.c.v. guide cannula for infusion was implanted. Stereotaxic coordinates were 1.5 mm posterior to bregma, 1 mm right of the midline. The guide cannula was implanted 1.7 mm ventral to the superior surface of the skull and fixed with jeweler's acrylic cement. Experiments were performed 48 h after surgery. I.c.v. treatments were performed with a 30-gauge cannula, which was fitted into the guide cannula and connected by a polyethylene tube to a micro syringe. The tip of the infusion cannula protruded 1 mm beyond the guide cannula, aiming the right lateral brain ventricle.

2.4. QA-induced seizures

An i.c.v. QA infusion of 9.2 mM (4 μl), the lowest dose that cause seizures in all animals, was performed in the study group. The control group received 4 μl of vehicle. Mice were observed for 10 min in Plexiglas chambers to detect tonic–clonic seizures lasting more than 5 s. Latency and duration of seizures, and mortality after seizure were also evaluated. We considered protection against seizure when the animals did not present seizures in 10 min. After the experiments, the dye methylene blue (4 μl) was injected through the cannula to identify the site of injection. Animals without the dye in the lateral brain ventricle were discarded (Schmidt et al., 2000).

2.5. Treatments

We performed i.c.v. administration of INO, DZ (agonist of BZ) and ADO and intraperitoneal (i.p.) administration of FLU (antagonist of BZ) and CAF (10 mg/kg – antagonist of A1 and A2a ADO receptors (Botton, et al. 2010; Cunha, et al. 2008).

The dose of 8 nmol DZ was chosen because of the maximal concentration to be dissolved in PBS + Tween, and the ability to promote anticonvulsant effect similar to INO against QA-induced seizures. The dose of FLU was based on previous studies showing the antagonistic effect of FLU against DZ anticonvulsant activity (Moreau et al., 1989).

2.5.1. Treatment 1

Mice received either 4 μl i.c.v. infusion of 100–400 nmol of INO (n = 12–15 per group), or 4 μl i.c.v. infusion of vehicle (PBS) (control group; n = 12) 5 min before QA injection. We could not use higher doses of INO because of its poor solubility.

2.5.2. Treatment 2

Mice received either 4 μl i.c.v. infusion of 400 nmol of INO (n = 12–15 per group), or 4 μl i.c.v. infusion of vehicle (PBS) (control group; n = 12–15). 1–10 min before QA injection.

2.5.3. Treatment 3

Mice received i.p. injection of either FLU (10 mg/kg) or PBS + Tween (10 ml/kg; control group). After 15 min, 4 μl i.c.v. injection of vehicle (PBS + Tween) or INO (400 nmol) or DZ (8 nmol) was performed and 5 min later seizures were induced by QA administration (n = 12–15).

2.6. Treatment 4

Mice received i.p. injection of either CAF (10 mg/kg) or PBS (10 ml/kg; control group). After 15 min, 4 μl i.c.v. injection of vehicle (PBS) or INO (400 nmol) or ADO (400 nmol) was performed and 5 min later seizures were induced by QA administration (n = 10–16).

2.7. Statistical analysis

Statistical analysis between groups was performed by the Fisher's exact test to evaluate the presence of seizures and death. We used Fischer's exact test instead of chi square test because some of the values in some categories were less than 5. Latency and duration of seizures were evaluated by ANOVA plus Duncan test. All results with $P<0.05$ were considered significant. The results were reported as mean ± SE.

3. Results

QA (i.c.v) induced seizures in all animals of control groups. PBS and/or PBS + Tween i.c.v. did not evoke any seizure by themselves. The latency and duration of the tonic–clonic seizures of control groups were 24.2 ± 6 s and 20.9 ± 5 s, respectively.

Fig. 1 shows that INO pretreatment protected mice against QA-induced seizures. The anticonvulsant effect was dose-dependent (A) and varied with the time of administration before QA (B). The strongest

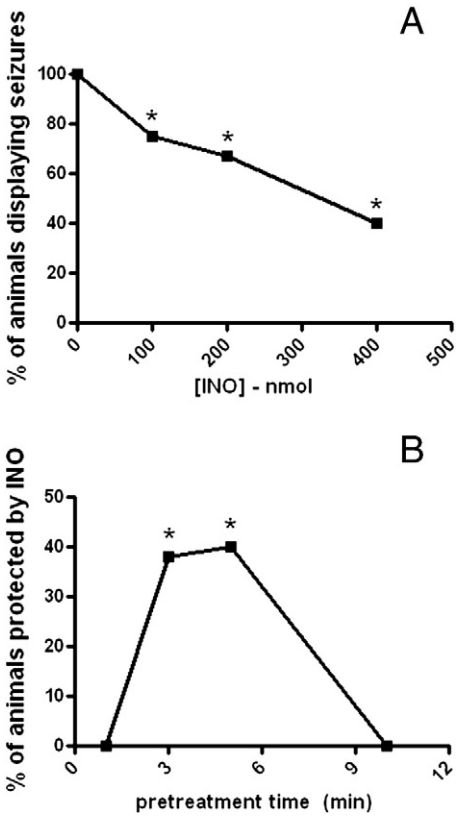

Fig. 1. Effect of dose (A) and pretreatment time (B) of INO against QA-induced seizures. A – Different doses of INO were administered i.c.v. 5 min before QA administration. B – INO 400 nmol were administrated i.c.v at different times before QA-induced seizures. After QA administration, mice were observed during 10 min for the occurrence of seizures. n = 12–15 animals per group. $P \leq 0.05$ (Fisher's exact test). * Different from control group.

anticonvulsant effect (protecting 60% of the animals) was observed with the administration of 400 nmol INO, 3 min before QA infusion.

Fig. 2 shows that DZ (8 nmol, i.c.v.), like INO (400 nmol, i.c.v.), partially prevented QA-induced seizures, while FLU (10 mg/kg, i.p.) had no effect. Moreover, FLU pretreatment (10 mg/kg, i.p., 15 min before INO or DZ injection) did not alter the anticonvulsant effect of INO, but abolished the anticonvulsant effect of DZ.

Fig. 3 shows that ADO (400 nmol, i.c.v.), like INO (400 nmol, i.c.v.), partially prevented QA-induced seizures, while CAF (10 mg/kg, i.p.)

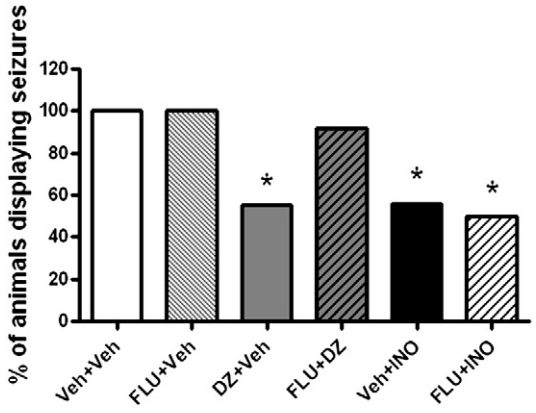

Fig. 2. FLU effect on INO or DZ anticonvulsant potential against QA-induced seizures. FLU or vehicle (PBS + Tween) was i.p. injected 15 min before INO (400 nmol) or DZ (8 nmol) or vehicle i.c.v. administration. Seizures were induced by i.c.v. QA infusion 5 min after INO or DZ or vehicle infusion and mice were observed for the occurrence of seizures; n = 12–15 per group. $^*P \leq 0.05$ (Fisher's exact test), as compared to control, FLU + Veh and FLU + DZ groups.

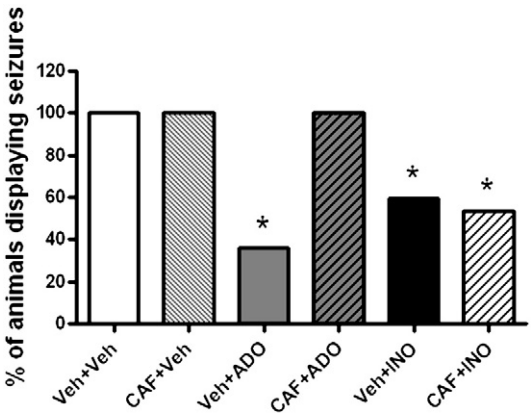

Fig. 3. CAF effect on INO or ADO anticonvulsant potential against QA-induced seizures. CAF or vehicle (PBS) was i.p. injected 15 min before INO (400 nmol) or ADO (400 nmol) or vehicle i.c.v. administration. Seizures were induced by i.c.v. QA infusion 5 min after INO or ADO or vehicle infusion and mice were observed for the occurrence of seizures; n = 10–16 per group. $^*P \leq 0.05$ (Fisher's exact test), as compared to control, CAF + Veh and CAF + ADO groups.

had no effect. Additionally, CAF pretreatment (10 mg/kg, i.p., 15 min before INO or DZ injection) did not modify the anticonvulsant effect of INO, but abolished the anticonvulsant effect of ADO.

Of note, none of the drugs tested here (INO, ADO, DZ, FLU or CAF) changed the pattern of seizures (onset, severity or duration). Additionally, we did not observe any sedative effects after i.c.v. injection of INO, ADO or DZ, nor hyper locomotion activity after i.p. administration of CAF. Moreover, no remarkable behavior was observed after administration of the drugs here used.

4. Discussion

The results of the present study clearly demonstrate an anticonvulsant effect of INO against QA-induced seizures in adult mice. To our knowledge, these results are the first evidence that INO is anticonvulsant against hyperactivation of the glutamatergic system in the CNS. The anticonvulsant effect of INO was previously demonstrated in models of acute seizures based on inhibition of GABA-A receptor complex. It is noteworthy that many different animal models may reflect a diversity of seizures etiology (Siniatchkin and Koepp, 2009). Thus, our results expand the prophylactic anticonvulsant potential of INO to another mechanism involved on seizures etiology.

Here we demonstrated that INO exhibited an anticonvulsant effect by central administration. Moreover, this effect (1) is dose dependent, (2) is similar to ADO (a well know purine with anticonvulsant effect), and (3) displays a narrow prophylactic profile (since it only begins to affect seizures when applied 3 min before triggering the seizures and it is no longer active when applied 10 min before triggering the seizures).

Our results suggest that the anticonvulsant activity of INO may act more against seizures evoked by hyperexcitation than those evoked by decreasing the inhibitory tonus of the CNS. The anticonvulsant effect of INO on models of acute seizures induced by QA- and PTZ were very similar regarding the dose and time of INO infusion. However, the seizure behaviors were completely blocked by INO when seizures were induced by QA infusion while only the latency to seizure were increased in the PTZ model (Skolnick et al., 1979).

To our knowledge, only few studies have investigated INO effects on excitatory synaptic transmission in brain circuits. Noteworthy, Shen et al. (2005) have demonstrated that microinjection of INO reversibly antagonized electrophysiological excitation by glutamate in cerebral cortical neurons. Additionally, it was already demonstrated that INO was also able to inhibit excitability in cultured spinal neurons (MacDonald et al., 1979). Moreover, INO was able to inhibit Purkinje cell activity (Bold et al., 1985). These studies support the hypothesis that INO may

act as an inhibitory neuromodulator against excitability, which could be implicated in the anticonvulsant effect. However, until now none specific receptor for INO has been identified on the CNS cell membrane.

Several studies have proposed that INO effects could be mediated by activation of BZ receptors based upon *in vitro* evidences that INO is able to displace BZ agonists binding to the CNS cell membrane (Marangos et al., 1979; Marangos et al., 1981c; Skolnick et al., 1979). In the present study, INO anticonvulsant effect did not seem to be mediated by activation of BZ receptor, since FLU did not block INO effect while completely abolished the DZ anticonvulsant action. To our knowledge, our study was the first to investigate whether a BZ antagonist could be able to block INO effect.

The anticonvulsant effect of INO could also be mediated by activation of ADO receptors. Recently, it was recognized that INO can also binds directly to A1, the main ADO receptor involved with the ADO anticonvulsant effect (Avsar and Empson, 2004; Dragunow and Faull, 1988; Fedele et al., 2006; Young and Dragunow, 1994). However, we could not confirm this hypothesis with our present results since CAF did not alter INO, but disrupted ADO anticonvulsant effect.

Taken altogether, neither BZ nor ADO receptors seems to be involved with the anticonvulsant effect reported here, suggesting that INO may exhibit an independently mechanism of action. Importantly, there was no attempt in the present work to explore an additive anticonvulsant effect of INO administration by activation of BZ and/or ADO receptors. This point should be explored in future works.

Our group has been studying for a long time the potential anticonvulsant effect of guanine based purines (Schmidt and Souza, 2010). We have previously demonstrated that GTP, GDP and GMP, and the nucleoside guanosine (GUO) present anticonvulsant effect against QA-induced seizures. We have reported that the anticonvulsant effect of the guanine based nucleotides depends on its conversion to GUO (Soares et al., 2004). Since GUO and INO have similar molecular structures and they share several cellular metabolic pathways, we can speculate that INO anticonvulsant effect may involve pathways also recruited by guanosine. Searching for neurochemical parameters involved in the GUO effects, we have demonstrated that GUO stimulates astrocytic glutamate uptake, which may be involved with its anticonvulsant action (Frizzo et al., 2003, 2001, 2005). However, there are no evidences that INO could modulate astrocytic glutamate uptake. So, further studies are necessary to clarify this hypothesis.

In summary, to our knowledge, this is the first study reporting the anticonvulsant effect of INO against QA induced seizures. Here we reported the potential prophylactic effect of INO against hyperactivation of the glutamatergic system. Further studies will be required to define the mechanisms of INO to control seizure activity and to investigate its potential therapeutic effect.

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