ELSEVIER

Brain Research 802 (1998) 55–60

BRAIN RESEARCH

Research report

Pharmacological evidence for GABAergic and glutamatergic involvement in the convulsant and behavioral effects of glutaric acid

Telmo Tiburcio Fortes Lima [a], Jairo Begnini [a], Juliano de Bastiani [a], Daniel Borges Fialho [a], Alexandre Jurach [a], Marinei Cristina Pereira Ribeiro [a], Moacir Wajner [b], Carlos Fernando de Mello [a,*]

[a] *Departamento de Química, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, 97105-900, Santa Maria, RS, Brazil*
[b] *Departamento de Bioquímica, Instituto de Ciências Básicas da Saúde, Universidade Federal do Rio Grande do Sul, 90105-900, Porto Alegre, RS, Brazil*

Accepted 19 May 1998

Abstract

The effect of intrastriatal administration of glutaric acid (GTR), a metabolite that accumulates in glutaric acidemia type I (GA-I), on the behavior of adult male rats was investigated. After cannula placing, rats received unilateral intrastriatal injections of GTR buffered to pH 7.4 with NaOH or NaCl. GTR induced rotational behavior toward the contralateral side of injection and clonic convulsions in a dose-dependent manner. Rotational behavior was prevented by intrastriatal preadministration of DNQX and muscimol, but not by the preadministration of MK-801. Convulsions were prevented by intrastriatal preinjection of muscimol. This study provides evidence for a participation of glutamatergic non-NMDA and GABAergic mechanisms in the GTR-induced behavioral alterations. These findings may be of value in understanding the physiopathology of the neurological dysfunction in glutaric acidemia.

Keywords: Glutaric acid; Organic acidemia; Neurotoxicity; GABA; Glutamate; Seizure; Turning behavior; Striatum

1. Introduction

Increased glutaric acid (GTR) levels in serum and brain are the major biochemical findings observed in glutaric acidemia type I [11,14].

Glutaric acidemia type I (GA-I) is an inherited pathological condition that results from the impairment in lysine and tryptophan oxidation, caused by a severe deficiency of glutaryl-CoA dehydrogenase (EC 1.3.99.7) activity. It is clinically characterized by progressive dystonia, dyskinesia, seizures and failure to thrive and, pathologically by striatal degeneration [11,15]. Neurochemical alterations in this disease include a decrease of γ-aminobutyric acid (GABA) levels in the caudate and putamen nuclei, probably due to glutamic acid decarboxylase (GAD) inhibition by GTR, 3-OH glutaric or glutaconic acid [29]. Administration of Vigabatrin (γ-vinyl–GABA), an irreversible inhibitor of GABA transaminase, to a glutaric acidemic patient improved cerebrospinal fluid free GABA levels and dystonia, suggesting that neurologic abnormalities may be related to low GABA levels [10].

Although some metabolic effects of GTR have been described, the mechanisms underlying the neurotoxic effects of this acid in this acidemia are poorly known to date. GTR has been demonstrated to be toxic to striatal cells in culture [30], and evidence has been gathered indicating that glutamatergic mechanisms may be a final common pathway for neurologic disorders [17]. GTR is structurally related to glutamate (Fig. 1) and inhibits glutamate (GLU) uptake in vitro [4] causing extracellular glutamate accumulation. Since glutamate accumulation due to chronic inhibition of uptake causes a slow rate of neuronal loss in rat spinal cultures [26], it is tempting to propose this mechanism of action for the neurotoxic effects of GTR.

In the present study we investigated the effect of intrastriatal injection of GTR on adult rat behavior, aiming to evaluate the acute consequences of cerebral accumulation of this organic acid. Moreover, the involvement of gluta-

* Corresponding author. Fax: +55-55-226-8031; E-mail: cfmello@base.ufsm.br

0006-8993/98/$19.00
PII: S0006-8993(98)00563-0

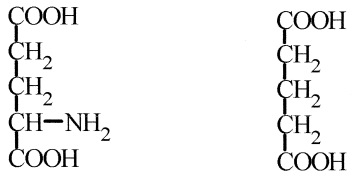

Fig. 1. Molecular structure of glutamic acid and glutaric acid.

matergic and GABAergic mechanisms in the behavioral effects observed was investigated.

2. Material and methods

2.1. Animals and reagents

Adult male Wistar rats (270–300 g) maintained on a 12:12 h light/dark cycle with free access to tap water and standard lab chow (Guabi, Santa Maria, RS, Brazil), were used, and each animal was used only once.

All reagents were purchased from Sigma (St. Louis, MO) except MK-801 (dizocilpine maleate) which was purchased from RBI (Natick, MA).

2.2. Behavioral evaluation

Animals were anesthetized with pentobarbital and placed in a rodent stereotaxic apparatus. Under stereotaxic guidance, a cannula was inserted unilaterally into the striatum (coordinates relative to bregma: AP 0 mm, ML 3.0 mm, V 4.0 mm from the dura). Chloramphenicol (200 mg/kg i.p.) was administered immediately before the surgical procedure. Three days after cannula placing, the animals were injected with 2 μl GTR (0.4–4 μmol) or NaCl (11 μmol). GTR solutions were buffered with NaOH to pH 7.4 and injections were performed over a 2 min interval. The solution containing maximal glutaric acid concentration and the NaCl solution were isosmotic. Immediately after the injections the animals were transferred to a round open field (54.7 cm diameter) with a floor divided into 11 equal areas. The open field session lasted 20 min, and during this time the animals were observed for the appearance of clonic or tonic–clonic convulsions, wet dog shakes and rotational responses. A rotational response was considered as a 360° movement comprising no more than three areas. The number of ipsilateral and contralateral rotational responses to the site of injection, wet dog shakes, clonic convulsions and duration of convulsions were recorded. In those experiments designed to evaluate the participation of glutamatergic mechanisms in GTR-induced behavioral effects, the animals were preinjected with 0.5 μl saline (0.9% NaCl), MK-801 (3 or 10 nmol) or DNQX (6,7-dinitroquinoxaline-2,3-dione) (8 nmol) and injected with 1.5 μl GTR (3 μmol) or NaCl (8.25 μmol) 40 min later. The involvement of GABAergic mechanisms in the behavioral effects of GTR was investigated by preinjecting muscimol (46 pmol), as described for the glutamatergic antagonists.

2.3. Statistical analysis

Statistical analysis was carried out by One- or Two-way analysis of variance (ANOVA) and F values are presented only if $p < 0.05$. Post-hoc analysis was carried out when appropriate using the Student–Newman–Keuls test. The dose-effect relationship was assessed using the Pearson's correlation coefficient.

3. Results

The effect of intrastriatal GTR administration on the number of contralateral rotations is shown in Fig. 2. Statistical analysis (One-way ANOVA) revealed that GTR increased the number of contralateral rotations [$F(3,28) = 4.94$; $p < 0.01$] in a dose-dependent manner (Pearson's correlation coefficient = 0.457; $p < 0.05$), but had no effect on the number of ipsilateral rotational responses (data not shown). Intrastriatal GTR administration induced seizure activity measured by number [$F(3,28) = 5.86$; $p < 0.005$; Pearson's correlation coefficient = 0.482; $p < 0.05$; Fig. 3] and total duration of convulsion episodes [$F(3,28) = 6.24$; $p < 0.005$; Pearson's correlation coefficient = 0.571; $p < 0.05$; Fig. 4] in a dose-dependent manner. The administration of an intermediate dose (1.3 μmol) of GTR

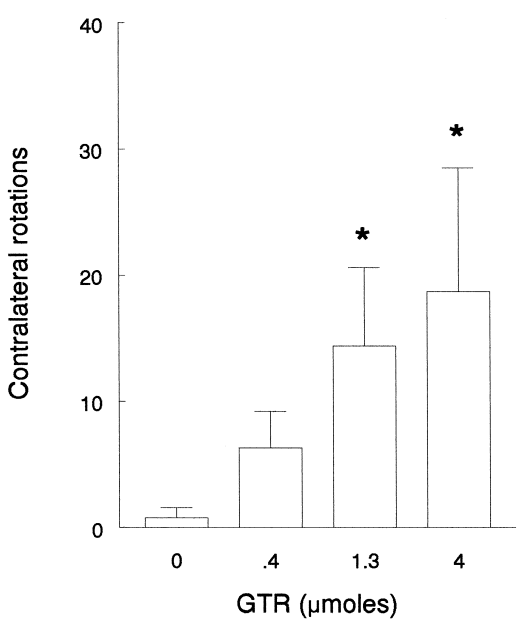

Fig. 2. Number of contralateral rotations induced by intrastriatal GTR (2 μl/striatum). * $P < 0.05$ compared to NaCl by the Student–Newman–Keuls test. Data are mean + S.E.M. for $n = 6–7$ per group. The results of One-way ANOVA are shown in the text.

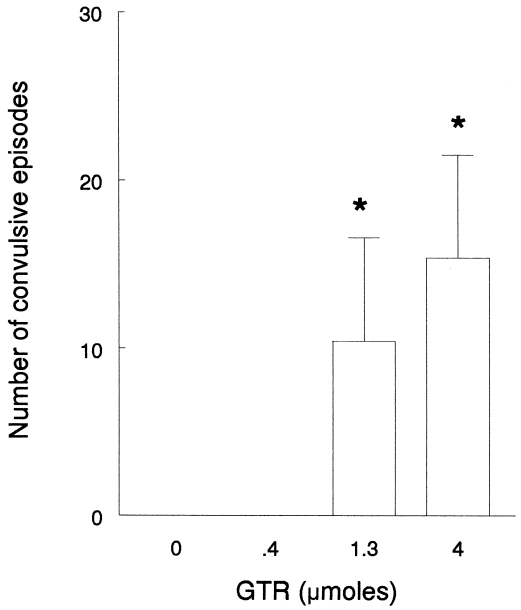

Fig. 3. Number of convulsive episodes induced by intrastriatal GTR (2 μl/striatum). * $P < 0.05$ compared to NaCl by the Student–Newman–Keuls test. Data are mean + S.E.M. for $n = 6–7$ per group. The results of One-way ANOVA are shown in the text.

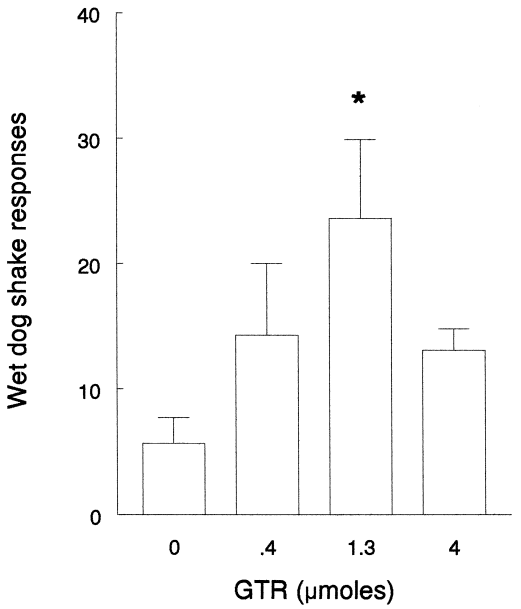

Fig. 5. Number of wet dog shake-like responses induced by intrastriatal GTR (2 μl/striatum). * $P < 0.05$ compared to NaCl by the Student–Newman–Keuls test. Data are mean + S.E.M. for $n = 6–7$ per group. The results of One-way ANOVA are shown in the text.

increased the number of wet dog shake-like responses [$F(3,28) = 3.79$; $p < 0.05$; Fig. 5]. This result is consistent with the view that the 'wet dog shake' behavior is a preconvulsant behavior [5,19].

It is well established that glutamate agonist administration into the dorsal striatum induces contralateral turning behavior [2,16,20,25]. Moreover, picrotoxin, a GABA antagonist, induces a similar behavioral response when injected into this region [28], and both classes of drugs have been demonstrated to elicit convulsions when administered into a wide range of cerebral structures, including the striatum and hippocampus [23]. In addition, it has been demonstrated that GTR inhibits glutamate decarboxylase activity, and may cause GABA depletion through this mechanism [11]. The resemblance between the behavioral effects of glutaric acid and those elicited by GABAergic antagonists and glutamatergic agonists led us to test whether these neurotransmitter systems were involved in the behavioral alterations observed.

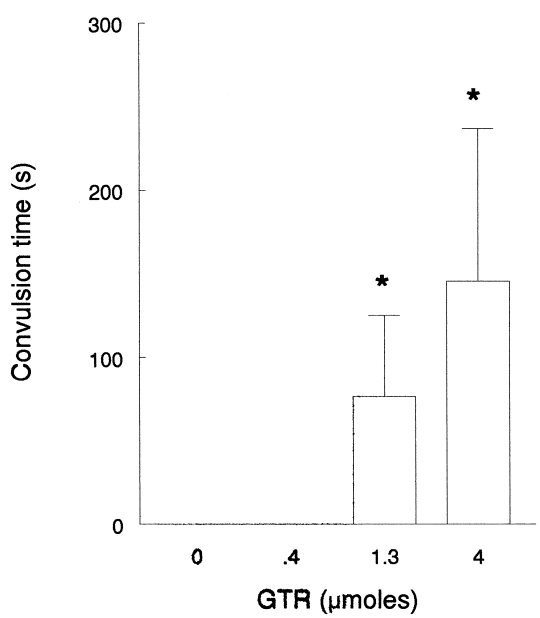

Fig. 4. Convulsion time elicited by intrastriatal GTR (2 μl/striatum). * $P < 0.05$ compared to NaCl by the Student–Newman–Keuls test. Data are mean + S.E.M. for $n = 6–7$ per group. The results of One-way ANOVA are shown in the text.

The involvement of glutamatergic NMDA (*N*-methyl-D-aspartate acid) receptors in the convulsant and rotational effects of GTR was investigated by pretreating the animals with MK-801 (3 or 10 nmol), a noncompetitive NMDA antagonist. Pretreatment with MK-801 (3 nmol) had no effect on the number of contralateral rotations, convulsive episodes and convulsion time elicited by glutaric acid. MK-801 (10 nmol), on the other hand, completely reversed glutaric acid-induced convulsions [significant pretreatment (MK-801 or saline) × treatment (NaCl or GTR) interaction: $F(1,55) = 5,81$; $P < 0,01$] and decreased GTR-induced rotational behavior [significant pretreatment (MK-801 or saline) effect: $F(1,55) = 5,92$; $P < 0,01$—data not shown]. Nevertheless, this dose of MK-801 caused a highly significant increase in the number of ipsilateral rotation responses [$F(1,55) = 8.66$; $p < 0.005$]. This prominent increase in the number of ipsilateral rotational responses indicates that the higher dose of the NMDA antagonist had an effect per se, that probably resulted from a decrease in the excitatory activity in the injected hemisphere. There-

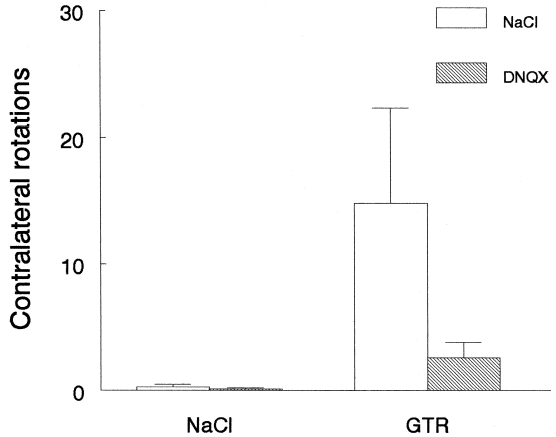

Fig. 6. Effect of DNQX (8 nmol/0.5 μl) on the number of contralateral rotational responses induced by GTR (3 μmol/1.5 μl). Data are mean + S.E.M. for $n = 9–10$ per group. The results of Two-way ANOVA are shown in the text.

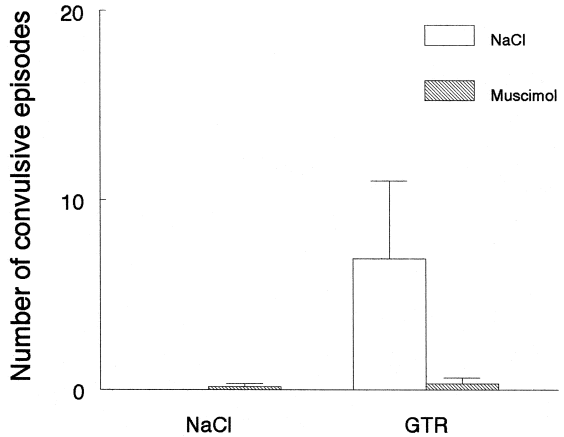

Fig. 8. Effect of muscimol (46 pmol/0.5 μl) on the number of convulsive episodes induced by GTR (3 μmol/1.5 μl). Data are mean + S.E.M. for $n = 9–10$ per group. The results of Two-way ANOVA are shown in the text.

fore, it is reasonable to ascertain that such a decrease in the excitatory tonus in the injected hemisphere may be responsible for the MK-801-induced decrease in the convulsive behavior, characterizing an antagonism of effect. Therefore, our data do not definitely support the involvement of NMDA mechanisms in these effects of GTR. On the other hand, DNQX (a non-NMDA antagonist) preadministration caused a decrease in the number of contralateral rotations induced by glutaric acid [significant pretreatment (DNQX or saline) × treatment (NaCl or GTR) interaction: $F(1,36) = 5,81$; $P < 0,05$; Fig. 6], but not in the convulsant action of glutaric acid (data not shown). It is important to point out that DNQX had no effect on the number of ipsilateral rotational responses, a fact that makes physiological antagonism an unlikely explanation for these results. These results suggest the involvement of non-NMDA glutamatergic receptors in the GTR-induced rotational behavior.

The involvement of GABAergic mechanisms in the convulsant and rotational effects of glutaric acid was investigated by pretreating the animals with muscimol (46 pmol), a $GABA_A$ agonist. This dose was chosen because it caused neither ipsilateral rotational behavior nor a decrease in motor activity in a pilot experiment. Muscimol pretreatment fully reversed the glutaric acid-induced contralateral rotational responses [significant pretreatment (muscimol or saline) × treatment (NaCl or GTR) interaction: $F(1,39) = 7,72$; $P < 0,05$; (Fig. 7) and glutaric acid-induced convulsions [significant pretreatment (muscimol or saline) × treatment (NaCl or GTR) interaction: $F(1,39) = 5,78$; $P < 0,05$; see Fig. 8] for number of convulsive episodes and significant pretreatment (muscimol or saline) × treatment (NaCl or GTR) interaction [$F(1,39) = 4.61$; $P < 0,05$; see Fig. 9] for duration of convulsive episodes. These results strongly support the involvement of GABAergic mechanisms in the behavioral and convulsant effects of glutaric acid.

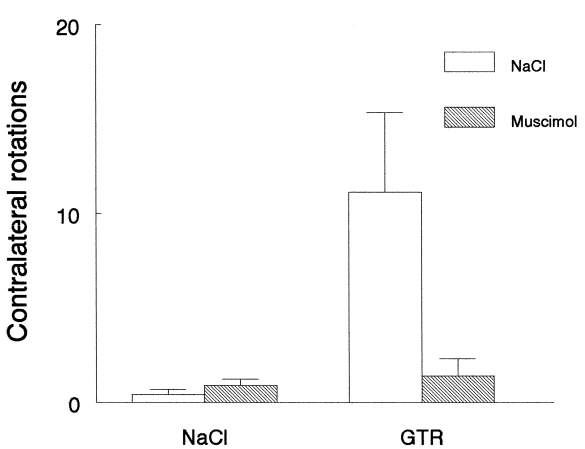

Fig. 7. Effect of muscimol (46 pmol/0.5 μl) on the number of contralateral rotational responses induced by GTR (3 μmol/1.5 μl). Data are mean + S.E.M. for $n = 9–10$ per group. The results of Two-way ANOVA are shown in the text.

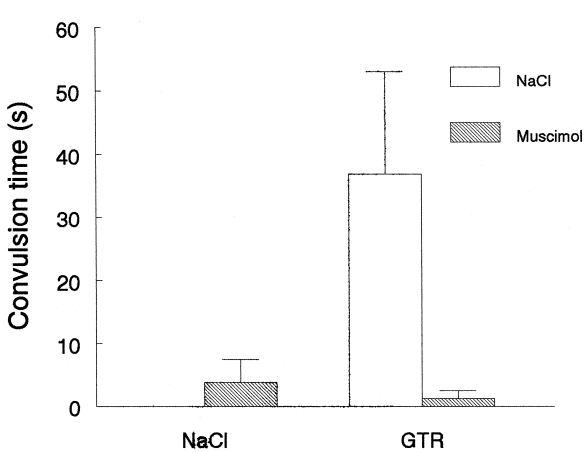

Fig. 9. Effect of muscimol (46 pmol/0.5 μl) on the convulsion time induced by GTR (3 μmol/1.5 μl). Data are mean + S.E.M. for $n = 9–10$ per group. The results of Two-way ANOVA are shown in the text.

4. Discussion

The striatum is a cerebral structure vulnerable to the neurotoxic action of several compounds. Sensitivity to these agents occurs because the striatum bears many glutamatergic receptors besides being highly susceptible to ischemia and neurotoxicity induced by metabolic inhibition and free radicals [8,18,21].

Several substances potentially toxic for the central nervous system have been studied by behavioral and histological evaluation after intrastriatal injections in the rat, including inhibitors of the enzyme succinate dehydrogenase [3,6,7,12,13,21,27,31,32]. In addition, a similar protocol was used by us to demonstrate that the behavioral effects of the succinate dehydrogenase inhibitor, methylmalonic acid, are mediated by glutamate [24].

The striatum is the most severely affected brain structure in glutaric acidemic children [11]. Since no animal models of glutaric acidemia have been described to date, the present study was conducted to evaluate the behavioral consequences of acute cerebral high levels of this organic acid in a cerebral structure that is exquisitely vulnerable in glutaric acidemia type I.

To our knowledge, the present work demonstrates for the first time the convulsant properties of glutaric acid. This is in agreement with the neurological alterations seen in children with glutaric acidemia who present convulsions besides dyskinesia, and suggests that GTR may cause an acute imbalance between inhibitory and excitatory mechanisms, leading to convulsion. The role of inhibitory (γ-aminobutyric acid; GABAergic) and excitatory (glutamatergic) neurotransmission in the genesis of convulsions and epilepsy has been recently reviewed by Meldrum [22], and a large body of evidence supports the view that convulsions may arise from either an impairment of GABAergic function or excessive glutamatergic function. This may be the case in the convulsive behavior elicited by acute intrastriatal administration of glutaric acid. Glutaric acid is structurally related to glutamate and has been reported to inhibit glutamate uptake in synaptosomes at 10 mM concentration, but not at 0.1 mM [1,4]. Since it is not known if 1.0 to 1.5 mM concentrations found in glutaric acidemic brain can inhibit glutamate uptake and thus cause high and possibly stimulatory concentrations of glutamate in the synaptic cleft [11], the role of glutamatergic mechanisms in the neurotoxic effects of GTR in GA-I remains to be determined. In the present study we report some evidence that non-NMDA glutamatergic mechanisms may be involved in the GTR-induced rotational behavior, since DNQX partially reversed this behavioral effect. However, the involvement of this mechanism in the convulsant action of this metabolite is not supported by our results. Although the tissue concentrations of GTR after intrastriatal administration are unknown, we may speculate that the high GTR concentration infused may have interfered with cellular glutamate uptake, and induce an increase in extracellular glutamate concentration, leading to an activation of excitatory mechanisms and consequently eliciting the behavioral effects observed. This explanation, however, seems unlikely, since it is expected that high glutamate concentrations would stimulate all glutamate receptors, including NMDA receptors. The presently reported lack of effect of MK-801 (at doses that have no effect per se) on the behavioral effects of GTR does not support the hypothesis of activation of NMDA receptor-mediated mechanisms.

Alternatively, GTR could selectively interact with non-NMDA glutamatergic binding sites, a fact that may explain the effects of DNQX on the behavioral actions of glutaric acid. However, an elegant study has recently described that GTR, 3-OH-GTR and glutaconic acid have no effect on glutamate receptor-mediated membrane currents in frog oocytes expressing glutamate receptor subtypes [9]. These interesting results suggest that GTR does not elicit physiological glutamate-mediated responses per se. The same study, however, also reported that glutamate antagonists were able to attenuate 3-OH-GTR-induced tissue disintegration in vitro, suggesting the involvement of excitotoxic mechanisms. From a pharmacological point of view, the results reported by Flott-Rahmel [9] are, to some extent, very similar to those obtained by our group, who has attributed a main role to the loss of inhibitory GABAergic input in the development of the excitotoxic process.

Systemic or intracerebral administration of glutamate decarboxylase inhibitors induces convulsions by blocking GABA synthesis [23]. Glutaric acid and the other metabolites that accumulate in GA-I, glutaconic and 3-hydroxyglutaric acids have been reported to competitively inhibit neuronal GAD [29], and decreased GAD activity and GABA levels have been reported in the basal ganglia from glutaric acidemic patients. However, it is not known if this enzyme inhibition could produce neuronal damage and loss, and decreased GABA levels and GAD activity in the striatum might be secondary to cell death due to other causes [11]. In the present study we demonstrate that the convulsant effects of glutaric acid are completely reversed by pretreating the animals with a very low dose of muscimol, a $GABA_A$ agonist, strongly suggesting that deficient GABAergic function may underlie the effects of glutaric acid. Due to the decrease in GABAergic tonus in patients with GA-I, it is possible that GAD inhibition is an important factor for the neurotoxicity of GTR through the induction of a 'hyperexcitability state' favoring excitotoxicity.

Acknowledgements

The authors thank Mr. Antoninho Macuglia for competent animal care and breeding. This study was supported by grants from FIPE-UFSM, FAPERGS, CNPq, FINEP and PRONEX-MCT (grant no. 76.97.1025.00). T.T.F. Lima and J. de Bastiani are the recipients of FAPERGS-BIC

fellowships. J. Begnini and A. Jurach are the recipients of CNPq-UFSM PIBIC fellowships, and M.C.P. Ribeiro is the recipient of a FIPE-UFSM fellowship.

References

[1] V.J. Balcar, G.A.R. Johnston, The structural specificity of the high affinity uptake of L-glutamate and L-aspartate by rat brain slices, J. Neurochem. 19 (1972) 2657–2662.
[2] B.M. Baron, M.W. Dudey, D.R. McCarty, F.P. Miller, I.J. Reynolds, C.J. Schimidt, Guanine nucleotides are competitive inhibitors of *n*-methyl-D-aspartate at its receptor both in vitro and in vivo, J. Pharmacol. Exp. Ther. 250 (1989) 162–169.
[3] M.I. Behrens, J. Koh, L.M.T. Canzionero, S.L. Sensi, C.A. Csernansky, D.W. Choi, Nitropropionic acid induces apoptosis in cultured striatal and cortical neurons, NeuroReport 6 (1995) 545–548.
[4] J.P. Bennett, W.J. Logan, S.H. Snyder, Amino acids as central nervous transmitters: The influence of ions, amino acid analogues, and ontogeny on transport systems for L-glutamic and L-aspartic acids and glycine into central nervous synaptosomes of the rat, J. Neurochem. 21 (1973) 1533–1538.
[5] M.L. Brines, A.D. Dare, N.C. Lanerrolle, The cardiac glycoside ouabain potentiates excitotoxic injury of adult neurons in rat hippocampus, Neurosci. Lett. 191 (1995) 145–148.
[6] E. Brouillet, B.G. Jenkins, B.T. Hyman, R.J. Ferrante, N.W. Kowall, R. Srivastava, D.S. Roy, M.F. Beal, Age-dependent vulnerability of the striatum to the mitochondrial toxin 3-nitropropionic acid, J. Neurochem. 60 (1993) 356–359.
[7] M. Erecinska, D. Nelson, Effects of 3-nitropropionic acid on synaptosomal energy and transmitter metabolism: relevance to neurodegenerative brain diseases, J. Neurochem. 63 (1994) 1033–1041.
[8] S.L. Fink, D.Y. Ho, R.M. Spolski, Energy and glutamate dependency of 3-nitropropionic acid neurotoxicity in culture, Exp. Neurol. 138 (1996) 298–304.
[9] B. Flott-Rahmel, C. Falter, P. Schluff, R. Fingherhut, E. Christensen, C. Jakobs, U. Musshoff, J.D. Fautec, T. Deufel, A. Ludolph, K. Ullrich, Nerve cell lesions caused by 3-hydroxyglutaric acid: A possible mechanism for neurodegeneration in glutaric acidaemia I, J. Inher. Metab. Dis. 20 (1997) 387–390.
[10] B. Francois, J. Jaeken, P. Gillia, Vigabatrin in the treatment of glutaric aciduria type I, J. Inher. Metab. Dis. 13 (1990) 352–356.
[11] S.I. Goodman, F.E. Frerman, Organic acidemias due to defects in lysine oxidation: 2-ketoadipic acidemia and glutaric acidemia, in: C.R. Scriver, A.L. Beaudet, W.S. Sly, D. Valle (Eds.), The Metabolic and Molecular Bases of Inherited Disease, 7th edn., McGraw-Hill, New York, 1995, pp. 1451–1460.
[12] J.G. Greene, J.T. Greenamyre, Characterization of the excitotoxic potential of the reversible succinate dehydrogenase inhibitor malonate, J. Neurochem. 64 (1995) 430–436.
[13] J.G. Greene, P.H. Porter, R.V. Eller, J.T. Greenamyre, Inhibition of succinate dehydrogenase by malonic acid produces an 'excitotoxic' lesion in rat striatum, J. Neurochem. 61 (1993) 1151–1154.
[14] G.F. Hoffmann, W. Meier-Augenstein, S. Stöckler, R. Surtees, D. Rating, W.L. Nyhan, Physiology and pathophysiology of organic acids in cerebrospinal fluid, J. Inher. Metab. Dis. 16 (1993) 648–669.
[15] M. Kyllerman, O.H. Skjeldal, M. Lundberg, I. Holme, E. Jellum, U. von Döblen, A. Fossen, G. Carlsson, Dystonia and dyskinesia in glutaric aciduria type I: clinical heterogeneity and therapeutic considerations, Movement Disorder Society 9 (1994) 22–30.
[16] P. Laudrup, H. Kitgaard, Metabotropic and ionotropic excitatory receptor agonists induce different behavioral effects in mice, Eur. J. Pharmacol. 250 (1993) 15–22.
[17] S.A. Lipton, P.A. Rosenberg, Excitatory amino acids as a final common pathway for neurologic disorders, N. Engl. J. Med. 330 (1994) 613–622.
[18] A.C. Ludolph, M. Riepe, K. Ullrich, Excitotoxicity, energy metabolism and neurodegeneration, J. Inher. Metab. Dis. 16 (1993) 716–723.
[19] S. Maione, C.S. Biggs, F. Rossi, L.J. Fowler, P.S. Whitton, A-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate receptors modulate dopamine release in rat hippocampus and striatum, Neurosci. Lett. 193 (1995) 181–184.
[20] J.W. McDonald, A.S. Fix, J.P. Tizzano, D.D. Schoepp, Seizures and brain injury in neonatal rats induced by 1*S*,3*R*-ACPD, a metabotropic glutamate receptor agonist, J. Neurosci. 13 (1993) 4445–4455.
[21] J.W. McDonald, D.D. Schoepp, Aminooxyacetic acid produces excitotoxic brain injury in neonatal rats, Brain Res. 624 (1993) 239–244.
[22] B.S. Meldrum, Neurotransmission in epilepsy, Epilepsia 36 (1995) S30–S35.
[23] B. Meldrum, Epileptic seizures, in: G.J. Siegel, B.W. Agranoff, R.W. Albers, P.B. Molinoff (Eds.), Basic Neurochemistry, 5th edn., Raven Press, New York, 1995, pp. 885–897.
[24] C.F. Mello, J. Begnini, R.E. Jiménez-Bernal, M.A. Rubin, J. De Bastiani, E.J. Costa, M. Wajner, Intrastriatal methylmalonic acid administration induces rotational behavior and convulsions through glutamatergic mechanisms, Brain Res. 721 (1996) 120–125.
[25] K. Ossowska, S. Wolfarth, Stimulation of glutamate receptors in the intermediate/caudal striatum induces contralateral turning, Eur. J. Pharmacol. 273 (1995) 89–97.
[26] J.D. Rothstein, L. Jin, M. Dykes-Hoberg, R.W. Kuncl, Chronic inhibition of glutamate uptake produces a model of slow neurotoxicity, Proc. Natl. Acad. Sci. USA 90 (1993) 6591–6595.
[27] A. Sacaan, J.A. Monn, D.D. Schoepp, Intrastriatal injection of a selective metabotropic excitatory amino acid receptor agonist induces contralateral turning in the rat, J. Pharmacol. Exp. Ther. 259 (1991) 1366–1370.
[28] J. Scheel-Kruger, Dopamine–GABA interactions: evidence that GABA transmits, modulates and mediates dopaminergic functions in the basal ganglia and the limbic system, Acta Neurol. Scand. 73 (1986) 9–49.
[29] O. Stokke, S.I. Goodman, P.G. Moe, Inhibition of brain glutamate decarboxylase by glutarate, glutaconate and β-hydoxyglutarate: explanation of the symptoms in glutaric aciduria?, Clin. Chim. Acta. 16 (1976) 411–515.
[30] W.O. Whetsell, The use of organotypic tissue culture for study of amino acid neurotoxicity and its antagonism in mammalian CNS, Clin. Neuropharmacol. 7 (1984) 452–456, (Suppl 1).
[31] U. Wüllner, A.B. Young, J.B. Penney, M.F. Beal, 3-nitropropionic acid toxicity in the striatum, J. Neurochem. 63 (1994) 1772–1781.
[32] G.D. Zeevalk, E. Derr-Yellin, W.J. Nicklas, NMDA receptor involvement in toxicity to dopamine neurons in vitro caused by the succinate dehydrogenase inhibitor 3-nitropropionic acid, J. Neurochem. 64 (1995) 455–458.