Amino Acids (2008) 34: 75–80
DOI 10.1007/s00726-007-0587-z
Printed in The Netherlands

Amino Acids

Taurine release in developing mouse hippocampus is modulated by glutathione and glutathione derivatives

R. Janáky[1], **C. A. Shaw**[2], **S. S. Oja**[1,3], and **P. Saransaari**[1]

[1] Brain Research Center, University of Tampere Medical School, Tampere, Finland
[2] Department of Ophthalmology and Physiology and Neuroscience Program, University of British Columbia, Vancouver, British Columbia, Canada
[3] The Centre for Laboratory Medicine and Department of Clinical Physiology and Nuclear Medicine, Tampere University Hospital, Tampere, Finland

Received June 9, 2007
Accepted July 8, 2007
Published online August 15, 2007;

Summary. Glutathione (reduced form GSH and oxidized form GSSG) constitutes an important defense against oxidative stress in the brain, and taurine is an inhibitory neuromodulator particularly in the developing brain. The effects of GSH and GSSG and glycylglycine, γ-glutamylcysteine, cysteinylglycine, glycine and cysteine on the release of [^{3}H]taurine evoked by K^+-depolarization or the ionotropic glutamate receptor agonists glutamate, kainate, 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and *N*-methyl-D-aspartate (NMDA) were now studied in slices from the hippocampi from 7-day-old mouse pups in a perfusion system. All stimulatory agents (50 mM K^+, 1 mM glutamate, 0.1 mM kainate, 0.1 mM AMPA and 0.1 mM NMDA) evoked taurine release in a receptor-mediated manner. Both GSH and GSSG significantly inhibited the release evoked by 50 mM K^+. The release induced by AMPA and glutamate was also inhibited, while the kainate-evoked release was significantly activated by both GSH and GSSG. The NMDA-evoked release proved the most sensitive to modulation: L-Cysteine and glycine enhanced the release in a concentration-dependent manner, whereas GSH and GSSG were inhibitory at low (0.1 mM) but not at higher (1 or 10 mM) concentrations. The release evoked by 0.1 mM AMPA was inhibited by γ-glutamylcysteine and cysteinylglycine, whereas glycylglycine had no effect. The 0.1 mM NMDA-evoked release was inhibited by glycylglycine and γ-glutamylcysteine. In turn, cysteinylglycine inhibited the NMDA-evoked release at 0.1 mM, but was inactive at 1 mM. Glutathione exhibited both enhancing and attenuating effects on taurine release, depending on the glutathione concentration and on the agonist used. Both glutathione and taurine act as endogenous neuroprotective effectors during early postnatal life.

Keywords: Glutathione – Glutathione derivatives – Taurine release – Neuroplasticity – Hippocampal slices – Developing mice

Abbreviations: AMPA, 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; BBB, blood–brain barrier; CNS, central nervous system; GABA, γ-aminobutyric acid; GSH, reduced glutathione; GSSG, oxidized glutathione; HEPES, *N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid; KA, kainate; mGluR, metabotropic glutamate receptor; NMDA, *N*-methyl-D-aspartate

Introduction

Taurine (2-aminoethanesulfonic acid) is a simple sulfur-containing inhibitory amino acid ubiquitous in virtually all animal cells. It is present at high concentrations in the brain; especially during ontogenic development its concentration exceeds that of the main excitatory transmitter glutamate (Saransaari and Oja, 2000). Taurine is a vital nutrient for cats (Sturman et al., 1985; Sturman, 1993) and immature primates (Neuringer et al., 1985; Devreker et al., 1999). It has an ancient osmoregulatory role in aquatic animals (Simpson et al., 1959) and been considered to play a similar role in the brains of terrestrial animals (Walz and Allen, 1987; Pasantes-Morales et al., 1990; Schousboe et al., 1990). On the other hand, taurine increases membrane chloride conductance, causing hyperpolarization and inhibiting neuronal firing (Oja et al., 1977, 1990; Sergeeva and Haas, 2003). In the hippocampus, taurine, released most probably from interneurons, inhibits firing of the main pyramidal neurons, members of the hippocampal glutamatergic excitatory circuit (Taber et al., 1986). The osmoregulatory and neuroinhibitory actions of taurine may both thus affect neuronal development, differentiation and protection against hypoxic, oxidative and excitotoxic insults (Huxtable, 1992; Saransaari and Oja, 2000). Indeed, taurine regulates neuronal activity, particularly in the immature brain (Kontro and Oja, 1987a, b; Saransaari and Oja, 2000), and protects neural cells against the toxicity of excitatory amino acids in the hippocampus (French et al., 1986).

γ-Glutamylcysteinylglycine (GSH, reduced glutathione) is also an ancient molecule in phylogeny (Orlowski and Karkowsky, 1976; Lenhoff, 1998; Janáky et al., 1999, 2000, 2007). GSH and its oxidized dimer (GSSG) constitute the most important defense against oxidative stress and reactive oxygen species in both peripheral organs and brain (Janáky et al., 2007). The long-known antioxidant role of GSH has presently seen a renaissance and GSH is now being reconsidered for clinical use in different oxidative stress states and neuropsychiatric disorders such as Parkinson's and Alzheimer's diseases, chronic fatigue syndrome, schizophrenia and other diseases with an etiopathogenesis of excitotoxic neuronal damage (Janáky et al., 2007). The postulated neuromodulatory and neurotransmitter roles of GSH may be reflected in this neuroprotection (Shaw et al., 1996; Shaw, 1998; Janáky et al., 1998, 2000, 2007). Similarly to taurine, extracellular GSH is a prerequisite for normal neuronal development. These aspects strongly support the conception that GSH may act in the regulation of glutamatergic transmission in the central nervous system (Shaw, 1998; Janáky et al., 2000, 2007).

Since taurine and glutathione share several common features, the working hypothesis adopted here was that GSH could trigger its neuroprotective and plastic events not only by itself but also via modulation of taurine release from taurine-containing modulatory interneurons. To prove such possible collaboration in the developing hippocampus, we now studied the effects of glutathione and glutathione derivatives on the K^+- and excitatory amino acid-evoked release of taurine in slices from developing mice. The hippocampus was chosen for its vulnerability to excitotoxicity and for its involvement in many important physiological brain functions, e.g., learning and memory and regulation of emotions, sexual behavior and autonomous functions.

Materials and methods

Materials

Developing 7-day-old NMRI mice (Orion, Espoo, Finland) of both sexes were used in the experiments. All efforts were made to minimize both the suffering and the number of animals used. The experiments conformed to the European Community Directive for the ethical use of experimental animals and were approved by the Tampere University committee for animal experiments. [1,2-^{3}H]Taurine (specific radioactivity 0.93 PBq/mol) was obtained from Amersham International (Bristol, UK). All specific reagents were from Tocris Bioscience (Bristol, UK), except for reduced and oxidized glutathione and dipeptide derivatives of glutathione, which were from Sigma (St. Louis, MO). The amino acids and peptides tested were L-enantiomorphs. All compounds tested were soluble in superfusion medium at the concentrations used in the experiments.

Release experiments

Slices 0.4 mm thick weighing 15–20 mg were manually prepared with a tissue slicer of Stadie-Riggs type from the mouse hippocampi and used immediately after preparation. They were first preloaded for 30 min at 37 °C with 10 μM (50 MBq/l) [^{3}H]taurine in preoxygenated Krebs-Ringer-*N*-2-hydroxyethylpiperazine-*N*′-2-ethanesulfonic acid (HEPES) medium under O_2 and agitation. The standard medium contained (in mmol/l) NaCl 127, KCl 5, $CaCl_2$ 0.8, $MgSO_4$ 1.3, $NaHPO_4$ 1.3, HEPES 15, NaOH 11 and D-glucose 10 (pH 7.4). The slices were then transferred to 0.25 ml cups and (unless otherwise specified) superfused with the above medium at a rate of 0.25 ml/min for 50 min in a system in which freely floating shaken slices were kept under a continuous flow of oxygen in order to preserve their viability (Kontro and Oja, 1987a). The superfusion medium was pooled during the first 20 min, whereafter 2-min fractions (0.5 ml) were collected directly into small scintillation vials with a fraction collector. After superfusion the slices were weighed, homogenized in ice-cold 5% (w/v) trichloracetic acid solution and centrifuged, and the clear supernatants used for scintillation counting. The effluent samples were subjected to the same analyses.

Estimation of efflux rate constants

The curves depicting the release of labeled taurine from the slices were plotted as a function of time on the basis of the radioactivities remaining in the slices after superfusion and recovered in the collected superfusate fractions. The efflux rate constants of taurine for the time intervals of 20 to 30 min (k_1) (basal release) and 34 to 50 min (k_2) (stimulated release) were computed as negative slopes of the regression lines iteratively fitted to these logarithmically transformed data curves (Kontro and Oja, 1987a). For illustrative purposes some results were depicted as fractional release, i.e., in the radioactivity lost from the slices within 1 min expressed a percentage of the total radioactivity remaining in the slices.

Statistical calculations

The presence of statistically significant differences between the means was detected by variance analysis. Comparison of individual means to one common control (as indicated in the tables) was made using the critical values published by Owen (1962). A probability level of $P < 0.05$ or less was considered statistically significant.

Results

GSH and GSSG did not alter the basal release of taurine in the developing hippocampus (data not shown). On the other hand, the release proved fairly sensitive to the other effectors used. Fifty millimolar K^+ enhanced the release almost 9-fold (Table 1). Glutamate did not affect the K^+-stimulated release while GSH and GSSG were slightly attenuating. However, neither of these altered the time course of release (Fig. 1A). Of the glutamate agonists, NMDA (0.1 mM) was the most effective, almost as effective as 50 mM K^+ (Table 2). The onset of the effect of NMDA was slightly faster than that of K^+ stimulation (Fig. 1B). AMPA (0.1 mM), kainate (0.1 mM) and glutamate (1 mM) all caused about 5-fold stimulation (Table 2). GSH and GSSG (both 1 mM) enhanced kainate stimulation, attenuated AMPA stimulation and did not affect NMDA stimulation. However, the effect of NMDA was

Table 1. Modulation of K^+-evoked taurine release by glutamate and reduced and oxidized glutathiones from hippocampal slices from 7-day-old mice

Compound (mM)	Efflux rate constant k_2, % of control	
None (control)	100.0 ± 3.6	(8)
K^+ 50	$874.8 \pm 37.6^{*}$	(8)
+Glutamate 1	$886.9 \pm 48.6^{*}$	(4)
+GSH 1	$706.7 \pm 49.1^{a,*}$	(12)
+GSSG 1	$640.5 \pm 45.4^{b,*}$	(16)

The slices were preloaded for 30 min with 10 μM [^{3}H]taurine in standard Krebs-Ringer-HEPES medium and superfused first with this unsupplemented medium for 25 min. Reduced (GSH) and oxidized (GSSG) glutathione were applied at 25 min, followed by 50 mM K^+ at 30 min until the end at 50 min. Glutamate was applied at 30 min together with 50 mM K^+. The efflux rate constants k_2 were computed for the period of 34–50 min and given as percentages (±S.E.M.) of the control. The rate constants for the control efflux were the following: k_1 (20–30 min) $0.024 \pm 0.002 \times 10^{-3}$ min^{-1} and k_2 (34–50 min: $0.020 \pm 0.0016 \times 10^{-3}$ min^{-1} (mean ± S.E.M., $n = 8$). Numbers of independent experiments are in parentheses. Significance of differences from the control: $^{*}P < 0.01$, and from the K^+ stimulation: $^{a}P < 0.05$; $^{b}P < 0.01$

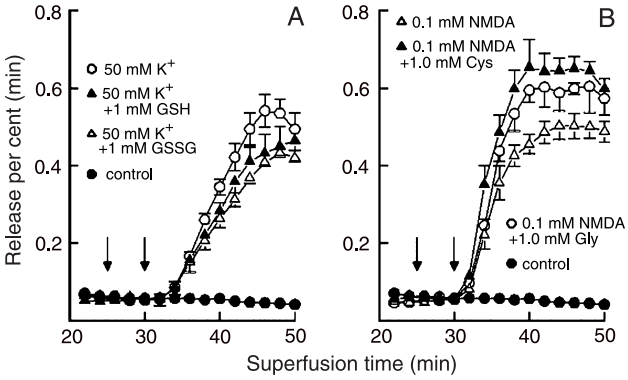

Fig. 1. A Effect of 50 mM K^+ on the release of [^{3}H]taurine from hippocampal slices from 7-day-old mice, and the effects of 1 mM reduced glutathione (*GSH*) and 1 mM oxidized glutathione (*GSSG*) on K^+-evoked release. **B** Effect of 0.1 mM *N*-methyl-D-aspartate (*NMDA*) on the release of [^{3}H]taurine, and the effects of 1 mM cysteine and 1 mM glycine on the NMDA-evoked release. The slices were preloaded for 30 min with 10 μM [^{3}H]taurine and superfused with this unsupplemented medium for 25 min. GSH, GSSG, cysteine or glycine were given at 25 min, followed by 50 mM K^+ or 0.1 mM NMDA at 30 min (arrows) until the end at 50 min. Mean values of 6–8 experiments are shown with S.E.M., if this exceeds the size of symbols

significantly reduced in the presence of 0.1 mM GSH or GSSG. Cysteine and glycine (both 1 mM) enhanced the NMDA effect (Table 2) without altering its time course (Fig. 1B). The 0.1 mM concentrations were ineffective. Of the dipeptides tested, γ-glutamylcysteine attenuated the effects of AMPA and NMDA, and glycylglycine did likewise with the NMDA effect. One millimolar cysteinylglycine attenuated the AMPA stimulation but did not influence the NMDA effect. However, 0.1 mM cysteinylglycine reduced the NMDA stimulation (Table 2).

Table 2. Modulation of glutamate-agonist-evoked taurine release by glutathione and glutathione derivatives from hippocampal slices from 7-day-old mice

Compound (mM)	Efflux rate constants k_2, % of the controls		Compound (mM)	Efflux rate constants k_2, % of the controls	
None (control a)	100.0 ± 3.6	(8)			
Glutamate 1 (control b)	$459.0 \pm 22.0^{a,**}$	(4)	NMDA 0.1 (control e)	$757.8 \pm 31.5^{a,**}$	(8)
+GSH 1	$363.6 \pm 31.2^{b,*}$	(4)	+GSH 0.1	$396.9 \pm 8.0^{e,**}$	(3)
+GSSG 1	$372.5 \pm 25.1^{b,*}$	(4)	+GSH 1	756.7 ± 48.2	(3)
Kainate 0.1 (control c)	$487.3 \pm 22.4^{a,**}$	(4)	+GSH 10	685.2 ± 36.6	(4)
+GSH 1	$600.5 \pm 25.1^{c,*}$	(4)	+GSSG 0.1	$495.9 \pm 28.0^{e,**}$	(3)
+GSSG 1	$678.8 \pm 20.3^{c,**}$	(4)	+GSSG 1	649.7 ± 64.8	(4)
AMPA 0.1 (control d)	$515.5 \pm 14.7^{a,**}$	(4)	+L-Cysteine 0.1	713.8 ± 42.0	(3)
+GSH 0.1	545.6 ± 8.9	(4)	+L-Cysteine 1	$1089.4 \pm 35.4^{e,**}$	(4)
+GSH 1	$386.8 \pm 29.0^{d,**}$	(4)	+Glycine 0.1	783.8 ± 32.0	(4)
+GSSG 0.1	618.9 ± 33.9	(4)	+Glycine 1	$895.8 \pm 51.5^{e,*}$	(3)
+GSSG 1	$457.1 \pm 18.1^{d,*}$	(4)	+Glycylglycine 1	$596.6 \pm 34.5^{e,**}$	(4)
+L-Cysteine 1	518.5 ± 16.6	(4)	+γGlutamylcysteine 0.1	$580.4 \pm 25.4^{e,**}$	(4)
+Glycine 1	$367.9 \pm 11.3^{d,**}$	(4)	+γ Glutamylcysteine 1	$449.3 \pm 15.5^{e,**}$	(4)
+Glycylglycine 1	584.9 ± 25.8	(4)	+Cysteinylglycine 0.1	$520.1 \pm 52.8^{e,**}$	(4)
+γ Glutamylcysteine 1	$319.6 \pm 20.3^{d,**}$	(4)	+Cysteinylglycine 1	770.9 ± 23.6	(4)
+Cysteinylglycine 1	$441.4 \pm 22.2^{d,*}$	(4)			

The results are given as in Table 1. Glutamate, AMPA, kainate and NMDA were applied at 30 min and all other effectors at 25 min until the end of superfusion. Significance of differences from the corresponding controls (a–e): $^{*}P < 0.05$; $^{**}P < 0.01$. *AMPA* 2-Amino-3-hydroxy-5-methyl-4-isoxazolepropionate; *NMDA* *N*-methyl-D-aspartate; *GSH* reduced glutathione; *GSSG* oxidized glutathione

Discussion

K^+ stimulation and the glutamate agonists, NMDA in particular, were highly effective in stimulating taurine release from hippocampal slices from developing mice. This result is in line with the data from earlier studies (Magnusson et al., 1991; Saransaari and Oja, 1997a, b, 2003; Oja and Saransaari, 2000). The effects of 50 mM K^+ and 1 mM glutamate on the release were not additive, indicating that their stimulative impact was apparently maximal. Our present results indicate that all classes of ionotropic glutamate receptors are involved. The transcripts encoding all subunits composing the NMDA, kainate and AMPA receptors are discernible postnatally in the rodent hippocampus, though their developmental patterns are different (Ritter et al., 2002). The greater efficacy of NMDA on taurine release is obviously due to the greater abundance of NMDA receptors in the developing hippocampus. Indeed, transient increases emerge in the expression of the various subtypes of NMDA receptors within one to three postnatal weeks in the rodent hippocampus (Pollard et al., 1993; Zhong et al., 1995; Dunah et al., 1996; Luo et al., 1996). In the developing hippocampus taurine release is also enhanced by activation of protein kinase C and adenosine receptor A_1 (Saransaari and Oja, 2003). Furthermore, the metabotropic glutamate receptors also influence taurine release, albeit less so than the ionotropic receptors (Saransaari and Oja, 1999).

GSH and GSSG (both 1 mM) significantly attenuated the K^+- and glutamate-evoked taurine release. The effects of GSH and GSSG on the release stimulated by the different agonists of glutamate receptors tested were not uniform. Those of kainate were enhanced and those of AMPA mostly attenuated. The effects on the NMDA-evoked release were seemingly peculiar: a low concentration of GSH and GSSG (0.1 mM) was inhibitory, but not the 1-mM and 10 mM concentrations. In keeping with this finding, Ca^{2+} influx into cultured cerebellar granule cells is affected in the opposite way by the same low and high concentrations of GSH. At a concentration of 0.1 mM GSH attenuates the influx of Ca^{2+}, while the enhancing effect is seen at the concentrations higher than 0.5 mM (Janáky et al., 1993). Furthermore, similar dualistic effects have been seen in the binding of dizocilpine to glutamate receptors in rodent cortical membranes. Both in the presence and absence of the co-activator glycine the effects of 0.1 mM and 1.0 mM GSH were the opposite (Janáky et al., 1998). Such paradoxic effects are probably due to the interference of GSH with NMDA receptors by means of its glutamate moiety at low concentrations, while at high concentrations the redox modulatory effects of GSH become more and more discernible. The findings of Ogita et al. (1995) also endorse this assumption.

Slice preparations contain both neurons and glial cells. The origin of taurine release could thus be either neuronal or glial. In the hippocampus, pyramidal basket interneurons, in which taurine is abundant, are a likely origin of neuronal taurine release (Taber et al., 1986). However, the contribution of glial cells to taurine release cannot be excluded, since functional ionotropic glutamate receptors are expressed in the two major macroglial cell types: astrocytes and oligodendrocytes (López et al., 1997; Condorelli et al., 1999; Bergles et al., 2000). The onset of K^+ stimulation of taurine release was delayed, a phenomenon also encountered in other brain preparations (Oja and Saransaari, 2000). This slow onset might be due to a predominant glial origin. On the other hand, the cytoarchitectural arrangement of astrocytes and oligodendroglial cells in the brain implies that opposite to the K^+-stimulated release neuronal glutamate-dependent signals can directly activate their receptors (Steinhäuser and Gallo, 1996), as the faster effects of glutamate agonists here show.

Taurine possesses specific functions during brain development, for example in functional maturation and cell migration in the cerebellum (Sturman et al., 1985; Sturman, 1993). It has also been shown to protect neural cells against many harmful and toxic effects (Oja and Saransaari, 2007). High-affinity glutamate-agonist-insensitive binding sites of glutathione exist in the brain (Janáky et al., 1999, 2000). A part of the effects of GSH and GSSG on taurine release may thus be mediated by the putative glutathione receptors by-passing the glutamate-receptor pathway. The cysteinyl moiety is crucial for the binding of glutathione to its receptors (Janáky et al., 1999). The efficacy of cysteine and cysteinyl dipeptides on the AMPA- and NMDA-evoked taurine release may be a sign of the involvement of these glutathione receptors. However, their existence, location and function have been characterized mainly in the cerebral cortex (Shaw et al., 1996; Janáky et al., 1999, 2000) and in the spinal cord (Lanius et al., 1993, 1994), but not yet in the hippocampus. Very recently, glutathione has been shown to activate the calcium-sensing receptor (Wang et al., 2006) which participates in the regulation of calcium homeostasis. The above-cited effects of glutathione on Ca^{2+} fluxes (Janáky et al., 1993) are of interest in view of this novel glutathione function. Since taurine also attenuates Ca^{2+} fluxes in the brain (Foos and Wu, 2002; El Idrissi and Trenkner, 2003; Wu et al., 2005), it may act in concert with glutathione in maintaining proper ionic homeostasis.

To sum up, the effects of glutathione on taurine release evoked by different ionotropic glutamate agonists in the hippocampus are somewhat complex, both enhancing and attenuating effects being discernible, depending on the effector concentrations and the type of the agonist. Both glutathione and taurine are neuroprotective in nature, but their actions may thus be either synergistic or antagonistic in the developing rodent hippocampus. At low extracellular (micromolar) concentrations glutathione inhibits taurine release evoked by NMDA receptors, the agonist of the predominant excitatory receptor at early postnatal age. In this manner it may affect the development of excitatory neural circuits in the hippocampus. On the other hand, at high (millimolar) concentrations glutathione enhances kainate-evoked taurine release being thus able to attenuate excitotoxic effects generated by this receptor class. The proper balance between taurine and glutathione may thus be crucial for both neural development and neuroprotection when developing neurons are sensitive to excitotoxins and the permeability of the blood-brain barrier is high and unselective.

Acknowledgments

This work was supported by grants from the competitive research funding of Pirkanmaa hospital district (9E112 and 9D099) to Réka Janáky and NSERC Canada and the US Army Medical Research and Material Command (DAMD17-02-1-0678) to Christopher A. Shaw. The skilful technical assistance of Ms. Oili Pääkkönen, Ms. Irma Rantamaa and Ms. Sari Luokkala is gratefully acknowledged.

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Authors' address: Prof. Simo S. Oja, Brain Research Center, Medical School, FI-33014 University of Tampere, Finland,
Fax: +358 3 3551 6170, E-mail: blsioj@uta.fi