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Glutamate-agonist-evoked taurine release from the adult and developing mouse hippocampus in cell-damaging conditions

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Summary. Taurine is a neuromodulator and osmoregulator in the central nervous system, also protecting neural cells against excitotoxicity. The effects of the ionotropic glutamate receptor agonists N-methyl-D-aspartate (NMDA), kainate and 2-amino-3-hydroxy-5-methyl-4-imidazolepropionate (AMPA) on [^{3}H]taurine release from hippocampal slices from 3-month-old and 7-day-old mice were studied in cell-damaging conditions. Neural cell injury was induced by superfusing the slices in hypoxic, hypoglycemic and ischemic conditions and by exposing them to metabolic poisons, free radicals and oxidative stress. The release of taurine was greatly enhanced in these conditions at both ages, except in oxidative stress. In normal conditions the three glutamate agonists potentiated taurine release in the immature hippocampus in a receptor-mediated manner, but kainate receptors did not participate in the regulation in the adults. The ability of the agonists to evoke taurine release varied in the cell-damaging conditions, but the glutamate-receptor-activated release was generally operating in the immature hippocampus. This glutamate-receptor-evoked massive release of taurine could have significant neuroprotective effects, particularly in the developing hippocampus, countering the harmful actions of the simultaneously liberated excitatory amino acids.

Keywords: Amino acids – Taurine release – Glutamate agonists – Cell damage – Tissue slices – Hippocampus

Introduction

Massive release of excitatory amino acids from neural structures during hypoxia and ischemia has been observed both in vitro (Pellegrini-Giampietro et al., 1990; Collard and Menon-Johansson, 1993; O'Regan et al., 1995) and in vivo (Benveniste et al., 1984; Hagberg et al., 1985; Globus et al., 1988). Excitatory amino acids are neurotoxic in excess and the resulting over-stimulation of their receptors contributes to neuronal death during cerebral

ischemia (see Rothman and Olney, 1988; Szatkowski and Attwell, 1994). The excitatory amino acids are partly released as a result of the action of oxygen-derived free radicals formed in hypoxic brain tissue (Pellegrini-Giampietro et al., 1988). Free radicals and excitatory amino acids cooperate in ischemia-induced neuronal damage (Pellegrini-Giampietro et al., 1990; Coyle and Puttfarcken, 1993). Of different brain areas, the hippocampus is particularly vulnerable to this kind of ischemic injury and subsequent cell death (Pulsinelli et al., 1992). It is particularly sensitive to excitotoxic agents in the newborn (Cook and Crutcher, 1986) but fairly well spared in hypoxia or ischemia (Cherubini et al., 1989; Ikonomidou et al., 1989; Ferriero et al., 1990). Since the most excitatory innervation in the hippocampus is glutamatergic, this vulnerability probably results from excitotoxicity mediated via glutamate receptors of the N-methyl-D-aspartate (NMDA) type (Zorumski and Olney, 1993), although the non-NMDA, kainate and 2-amino-3-hydroxy-5-methyl-4-imidazolepropionate (AMPA), receptors could also be involved (Choi and Rothman, 1990; Obrenovitch and Urenjak, 1997).

The inhibitory amino acid taurine has been held to have a special role in immature brain tissue (Oja and Kontro, 1983; Kontro and Oja, 1987). It appears to be essential for the development and survival of neural cells (see Huxtable, 1992; Sturman, 1993). Taurine also protects these cells against excitotoxicity induced by excitatory amino acids (French et al., 1986; Trenkner, 1990; Tang et al., 1996) and prevents harmful metabolic events induced by ischemia or hypoxia (Schurr et al., 1987). Furthermore, taurine-containing neurons are relatively inert in cerebral ischemia induced by 4-vessel occlusion (Wu et al., 1994). Taurine has long been known to ameliorate symptoms in epilepsy (Oja and Kontro, 1983). These neuroprotective effects may be related to the functions of taurine as a neuromodulator (Saransaari and Oja, 1992), osmoregulator, antioxidant and regulator of calcium ion movements (Oja and Kontro, 1983; Huxtable, 1992; Oja and Saransaari, 1996).

Taurine abounds in the hippocampus (Lombardini, 1976; Kontro et al., 1980) and taurine-like immunoreactivity is located in hippocampal interneurons, pyramidal neurons and dentate granule cells (Magnusson et al., 1989). Taurine inhibits the firing of hippocampal pyramidal neurons by increasing chloride conductance and causing hyperpolarization (Taber et al., 1986). The enzyme synthesizing taurine, cysteine sulphinate decarboxylase, has also been identified in pyramidal basket interneurons (Taber et al., 1986). Hippocampal taurine release is markedly enhanced in cell-damaging conditions such as hypoxia, hypoglycemia, ischemia and exposure to free radicals and oxidative stress (Saransaari and Oja, 1996; 1997a). It has also been demonstrated that the ionotropic glutamate receptor agonists NMDA, kainate and AMPA, evoke taurine release in both developing and adult hippocampus (Magnusson et al., 1991; Saransaari and Oja, 1994). We have now investigated how these ionotropic glutamate agonists evoke the release of preloaded [^{3}H]taurine from hippocampal slices from developing and adult mice in the above cell-damaging conditions.

Material and methods

Material

NMRI mice of both sexes aged 7 days and 3 months (adults), were used throughout. [1,2-^{3}H]Taurine (specific activity 1.07 PBq/mol) was obtained from Amersham International, Bristol, UK. Dizocilpine (MK-801) was a gift from Merck, Sharp & Dohme (Rahway, NJ).

Efflux experiments

Slices 0.4 mm thick weighing 15–20 mg were prepared from the hippocampi with a Stadie-Riggs tissue slicer and used immediately in efflux experiments. The slices were preloaded for 30 min with 10 μM (50 MBq/l) [^{3}H]taurine in preoxygenated Krebs-Ringer-Hepes-glucose medium under O_2 and then superfused as described in Kontro and Oja (1987). The medium was pooled during the first 20 min of superfusion and thereafter 2-min fractions (0.5 ml) were collected. The glutamate receptor agonists and antagonists were added at 30 min. 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 likewise counted for radioactivity.

Estimation of efflux rate constants

The release of labeled taurine from the slices was 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 (Kontro and Oja, 1987). The efflux rate constants of taurine for the time intervals of 20 to 30 min (k_1) and 34 to 50 min (k_2) were computed as negative slopes for the regression lines of the logarithm of radioactivity remaining in the slices vs. superfusion time.

Experimental conditions

Neural cell damage was induced by modifying experimental conditions from the beginning of superfusions. The medium for metabolic blockade contained 1.0 mM NaCN or 1.0 mM 2,4-dinitrophenol (DNP). In hypoglycemia, glucose was omitted from the medium and in hypoxia the medium was bubbled with N_2 gas for 1 h before and during the experiments. In ischemia, the glucose-free medium was bubbled with N_2 gas. Lipid peroxidation (Wills, 1969) (oxidative stress) was induced by $FeSO_4$ (7.5 μM) together with ascorbate (1.5 mM) (Agostinho et al., 1994). Free radical production was achieved by exposure to 0.01% hydrogen peroxide (Gilman et al., 1994).

Statistical calculations

The presence of statistically significant differences between the sample means was detected by variance analysis. Comparisons of individual means were made by Hartley's sequential method of testing.

Results

The glutamate receptor agonists NMDA, kainate and AMPA (all 0.1 mM) significantly potentiated the release of [^{3}H]taurine from hippocampal slices

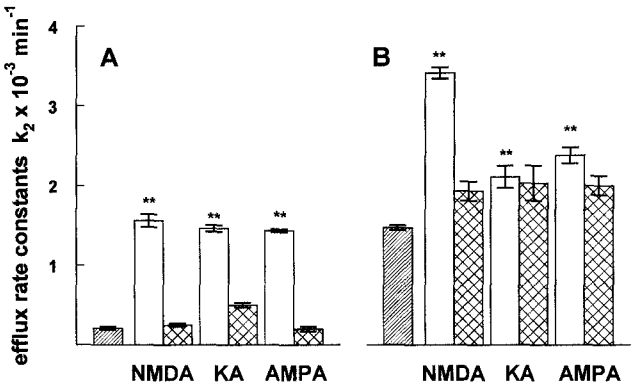

Fig. 1. Effects of ionotropic glutamate agonists (all 0.1 mM) NMDA, kainate and AMPA (open columns) on taurine release from hippocampal slices from 7-day- (**A**) and 3-month-old (**B**) mice in normoxic control conditions. The results are efflux rate constants (±SEM) k_2 for the time interval 34–50 min. The shaded columns depict control release without effectors. The cross-hatched columns represent the effects of NMDA, kainate and AMPA together with their respective antagonists MK-801, CNQX and NBQX (all 0.1 mM). The number of independent experiments is 4–8. Significance of differences from the control: $^{**}p < 0.01$

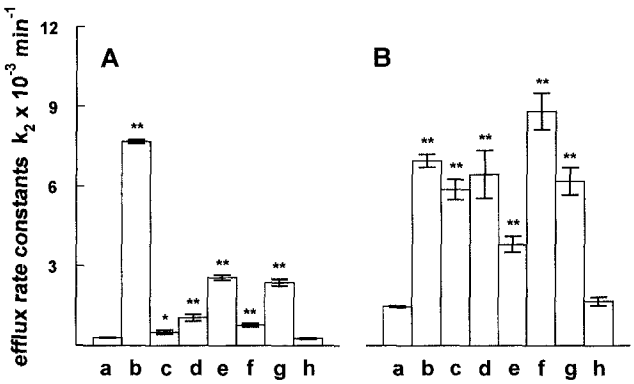

Fig. 2. Taurine release from hippocampal slices from 7-day- (**A**) and 3-month-old (**B**) mice in cell-damaging conditions. The results are mean efflux rate constants (±SEM) k_2 (34–50 min) of 4–8 independent experiments; (*a*) control release, and the effects of (*b*) 1.0 mM 2,4-dinitrophenol, (*c*) 1.0 mM NaCN, (*d*) hypoglycemia, (*e*) hypoxia, (*f*) ischemia, (*g*) free radicals and (*h*) oxidative stress. Significance of differences from the control: $^{*}p < 0.05$, $^{**}p < 0.01$

from both 7-day- and 3-month-old mice (Fig. 1). NMDA was the most potent at both ages. The effects of NMDA, kainate and AMPA were abolished by their antagonists MK-801, 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) and 6-nitro-7-sulphamoylbenzo[f]quinoxaline-2,3-dione (NBQX), respectively, only CNQX being unable to reduce the potentiation by kainate significantly in the adults (Fig. 1). All cell-damaging conditions, applied from the beginning

of superfusions, markedly enhanced taurine release, except for oxidative stress (Fig. 2). In the developing hippocampus 1.0mM DNP was the most potent, followed by hypoxia and exposure to free radicals. Ischemia was the most effective in the adults, but also DNP, hypoglycemia, free radicals and NaCN (1.0mM) evoked substantial taurine release.

The agonists NMDA, kainate and AMPA had no effect on taurine release in the presence of DNP (data not shown). In the presence of NaCN the agonists were also without effect in the adult hippocampus, but all three markedly potentiated taurine release in developing mice. These effects were abolished by the respective antagonists (Fig. 3). In hypoxic conditions the agonists were able to enhance taurine release in the immature hippocampus, the antagonists again blocking the effects (Fig. 4). In the adults kainate and AMPA were effective, their actions being reduced by CNQX and NBQX, respectively. In hypoglycemia and ischemia the agonists were unable to potentiate taurine release in the adult hippocampus, but in the immature hippocampus NMDA and kainate enhanced the release in hypoglycemia, which effects were blocked by MK-801 and CNQX, respectively (Fig. 5A, Fig. 6). Moreover, all agonists were effective in ischemic conditions in developing mice but the NMDA effect was not reduced by MK-801 (Fig. 5B). In free-radical-containing medium the agonists had no effects on taurine release, neither in the adult nor in the developing hippocampus (data not shown). On the other hand, all agonists potentiated the release under oxidative stress in both age groups. Their effects were antagonized by MK-801, CNQX and NBQX, except for the AMPA effect in the adults (Fig. 7).

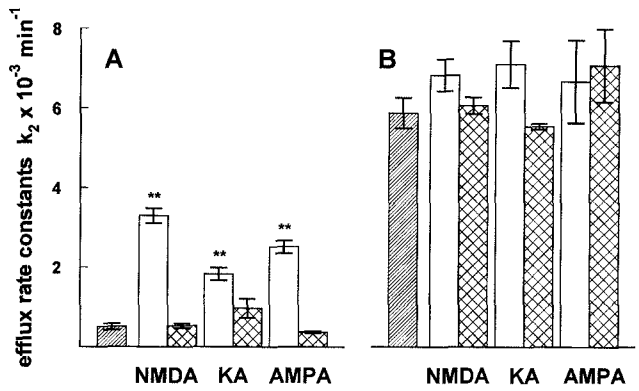

Fig. 3. Effects of NMDA, kainate and AMPA (open columns) (all 0.1mM) on hippocampal taurine release in 7-day- (**A**) and 3-month-old (**B**) mice in the presence of 1.0mM NaCN. The results are mean efflux rate constants (±SEM) k_2 (34–50min) of 4–8 independent experiments. The shaded columns represent control release and the cross-hatched columns the effects of the agonists together with their respective antagonists MK-801, CNQX and AMPA (all 0.1mM). Significance of differences from the control: $^{**}p < 0.01$

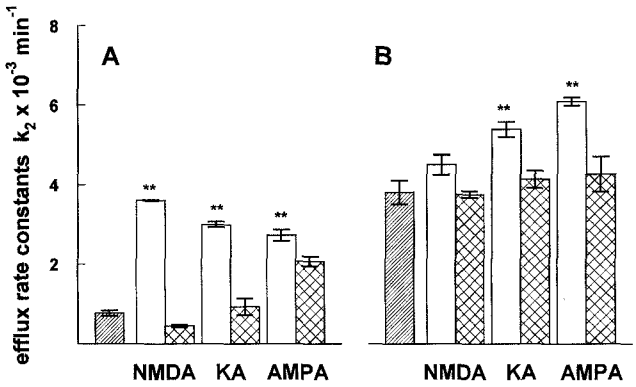

Fig. 4. Effects of NMDA, kainate and AMPA (open columns) (all 0.1 mM) on hippocampal taurine release in 7-day- (**A**) and 3-month-old (**B**) mice in hypoxic conditions. The results are mean efflux rate constants (±SEM) k_2 (34–50 min) of 4–8 independent experiments. The shaded columns represent control release and the cross-hatched columns the effects of the agonists together with their respective antagonists MK-801, CNQX and NBQX (all 0.1 mM). Significance of differences from the control: $^{**}p < 0.01$

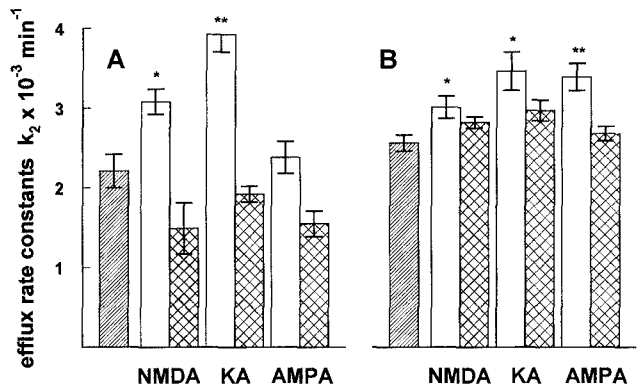

Fig. 5. Effects of NMDA, kainate and AMPA (open columns) (all 0.1 mM) on hippocampal taurine release in 7-day-old mice in hypoglycemia (**A**) and ischemia (**B**). The results are mean efflux rate constants (±SEM) k_2 (34–50 min) of 4–8 independent experiments. The shaded columns represent control release and the cross-hatched columns the effects of the agonists together with their respective antagonists MK-801, CNQX and NBQX (all 0.1 mM). Significance of differences from the control: $^{*}p < 0.05$, $^{**}p < 0.01$

Discussion

The hippocampal release of taurine was modified in both adult and developing mice by ionotropic glutamate receptors. NMDA, kainate and AMPA all markedly potentiated taurine release in the developing hippocampus, whereas the effects were considerably smaller in the adults. NMDA has generally been reported to be the most powerful agonist (Magnusson et al., 1991; Saransaari and Oja, 1991; 1994). The effects of kainate and AMPA were

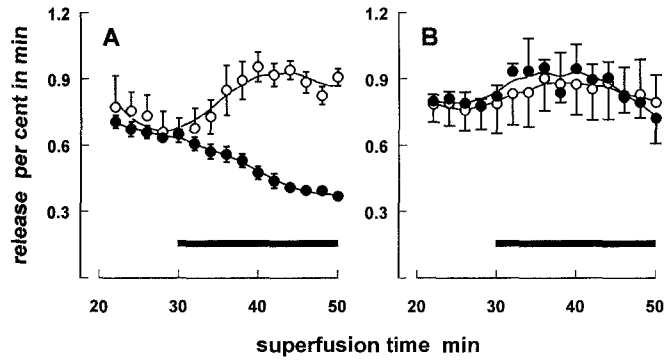

Fig. 6. Release of taurine from hippocampal slices from 7-day- (**A**) and 3-month-old (**B**) mice in hypoglycemia in the presence of 0.1 mM kainate (–o–) and 0.1 mM kainate together with 0.1 mM CNQX (–●–). The results are mean values ±SEM of 4 separate experiments. Kainate and CNQX were present in superfusion medium from 30 to 50 min, as indicated by the bar

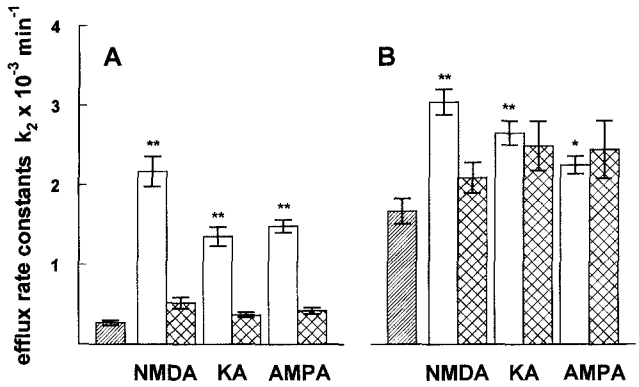

Fig. 7. Effects of NMDA, kainate and AMPA (open columns) (all 0.1 mM) on hippocampal taurine release in 7-day- (**A**) and 3-month-old (**B**) mice in medium inducing oxidative stress. The results are mean efflux rate constants (±SEM) k_2 (34–50 min) of 4–8 independent experiments. The shaded columns represent control release and the cross-hatched columns the effects of the agonists together with their respective antagonists MK-801, CNQX and NBQX (all 0.1 mM). Significance of differences from the control: *$p < 0.05$, **$p < 0.01$

abolished by the non-NMDA antagonists CNQX and NBQX, respectively, indicating that both types of receptors are involved in the evoked release of taurine in the immature hippocampus. The regulation by kainate receptors seems to be lost during maturation, since CNQX was unable to affect the kainate-evoked release in the adults. The inhibition of AMPA effects by NBQX implies the participation of AMPA receptors also in the adult hippocampus. The stimulation by NMDA was blocked by the specific antagonist MK-801 in both age groups. The occurrence of presynaptic NMDA-receptor-mediated release of taurine is corroborated by the finding that another potent NMDA receptor agonist, tetrazolylglycine (Schoepp et al.,

1991), has also enhanced taurine release in a dizocilpine-sensitive manner in both developing and adult mice (Saransaari and Oja, 1994). The operation of presynaptic glutamate receptors regulating the release of glutamate (Smirnova et al., 1993), together with that of other transmitters, including noradrenaline (Pittaluga and Raiteri, 1992a,b) and GABA (Janáky et al., 1993), has been demonstrated in the adult hippocampus. In the immature hippocampus, the agonists also potentiate GABA release in a receptor-mediated manner, implying the existence of presynaptic glutamate receptors regulating GABA release already during the early postnatal period (Saransaari and Oja, 1997b).

The ability of NMDA to evoke substantial release of taurine in the immature hippocampus tallies with the overexpression of the NMDA subtype of glutamate receptors in hippocampal formation during postnatal development (Tremblay et al., 1988; Represa et al., 1989; McDonald et al., 1990; Le Greves et al., 1996). The increase in the number of receptor sites also correlates with the development of afferent input and elaboration of dendrites in the hippocampus and with the developmental onset of long-term potentiation (Pokorny and Yamamoto, 1981a,b). During this period the number of kainate and AMPA binding sites is relatively low in the rat hippocampus, increasing only somewhat later (Ben-Ari et al., 1984; Insel et al., 1990; Miller et al., 1990). In rodents postsynaptic excitation consequently predominates over inhibition during the first weeks of life. This early developmental overexpression of NMDA receptors coincides with the increased susceptibility to seizures and excitotoxicity produced by excitatory amino acids (McDonald and Johnston, 1990). At this time the pronounced glutamate-receptor-activated release of taurine may be of great importance in counteracting excitotoxic effects and protecting against impending hyperexcitation.

Taurine is metabolically rather inert in the brain. The compound is not broken down (Huxtable, 1992) and the de novo synthesis is slow (Oja et al., 1973; Oja and Kontro, 1981). The blood-brain exchange rates are likewise low in both adult and developing rodent brain (Oja et al., 1976). The brain slices also maintain well their intracellular levels of taurine upon incubation in vitro, the slices from the developing brain in particular (Oja, 1971). The present qualitative differences in the responses to the glutamate receptor agonists and antagonists cannot be accounted for any differences in taurine metabolism in the two experimental groups. Although the taurine concentration in hippocampal slices is more than two times higher in 7-day-old than in 3-month-old mice, the spontaneous release of endogenous taurine is threefold in the latter (Saransaari and Oja, unpublished results). The preloaded [^{3}H]taurine is then mixed in adult mice with a smaller intracellular taurine pool that is more readily spontaneously releasable. The quantitative responses to the effectors are thus to some extent overshadowed by spontaneous taurine release in slices from the mature hippocampus.

The conditions known to cause neural cell damage (Haddad and Jiang, 1993; Hara et al., 1993) generally greatly enhanced taurine release. The marked increase in taurine release in cell-damaging conditions, particularly in ischemia, could be attributable to several mechanisms, including

Ca-dependent exocytosis, Ca-independent release via reversal of carrier-mediated uptake, indiscriminate opening of ion channels and unspecific leakage through damaged plasma membranes. This last alternative is not likely, however, since earlier investigations have shown that in hippocampal slices the liberation of lactate dehydrogenase (a common marker of plasma membrane damage and nonspecific lysis of neural cells) is not increased by the present type of ischemia (Pellegrini-Giampietro et al., 1990; Cherici et al., 1991). Neither could we now see any increase in lactate dehydrogenase in superfusion media under ischemic conditions in either age group (data not shown). An activation of volume-sensitive efflux could have contributed to taurine release (Schousboe et al., 1990). For example, brain slices swell under anaerobic conditions and in the presence of metabolic poisons (Laakso and Oja, 1976). Intracellular swelling activates stretch-sensitive ion channels and is generally accompanied by the release of both inorganic and organic osmolytes, including taurine (Pasantes-Morales et al., 1993). To date, nonsaturable diffusion of taurine is indeed known to be greatly enhanced in ischemic conditions (Saransaari and Oja, 1996).

The substantial increase in the release of taurine in ischemia and other cell-damaging conditions could be due partly to inhibition of reuptake. Taurine uptake by mouse cerebral cortical synaptosomes is in fact inhibited in most of the present cell-damaging conditions, most markedly in the adult brain (Saransaari and Oja, 1996). Although the medium is continuously renewed in superfusion experiments, taurine molecules released from the intracellular spaces must first traverse the extracellular space, being then subject to possible reuptake. Indeed, there is a significant positive correlation between the efflux and influx rates of taurine in brain slices in different experimental conditions (Oja and Saransaari, 1994). The enhanced release of excitatory amino acids in hypoxic and ischemic conditions (Lekieffre et al., 1992; Collard and Menon-Johansson, 1993; Globus et al., 1993) has also been thought to result from a reversed operation of cell membrane carriers (Szatkowski and Attwell 1994). The function of Na-dependent aturine carriers in cell plasma membranes is similarly reversible in certain experimental conditions (Korpi and Oja, 1983). The reversed action of sodium-dependent high-affinity taurine carriers, changing the direction of mediated transport, has thus apparently contributed to the present results.

The ability of ionotropic glutamate agonists to evoke taurine release varied in the different cell-damaging conditions. In the adults glutamate agonists were able to evoke release only in hypoxia and oxidative stress. Generally, the glutamate-receptor-stimulated release was operative in the immature hippocampus, except in the presence of DNP and free radicals, which agents as such already substantially potentiated the release. Free radicals are normal by-products of oxidative metabolism. Under certain conditions, including hypoxia and ischemia, free radical production may be excessively increased, damaging nervous system functions by disrupting membrane structures (Pelmar et al., 1989). Free radicals are also thought to be involved in many neurological disorders (Halliwell, 1992). Taurine release was greatly potentiated by exposure to media producing free radicals in both mature

and immature hippocampus, and the glutamate agonists failed to evoke any additional release. The release of glutamate has also been enhanced by exposure to peroxide-generated free radicals in rat hippocampal slices (Pellegrini-Giampietro et al., 1988, 1990), leading to extracellular accumulation of excitatory amino acids and contributing to excitotoxicity.

It is of particular note that in hypoxia, oxidative stress and metabolic blockade by NaCN, the activation of the three ionotropic glutamate receptors can enhance taurine release in the developing hippocampus. In ischemia the NMDA-induced release is apparently not receptor-mediated, since MK-801 was not able to antagonize it. Moreover, in hypoglycemia both NMDA and kainate receptors induced taurine release. This glutamate-receptor-evoked massive release of taurine could have significant neuroprotective effects in the immature hippocampus, countering in several ways the harmful actions of simultaneously liberated excitatory amino acids. Taurine inhibits the depolarizing effects of excitatory amino acids by increasing membrane chloride conductance (Oja et al., 1990). It attenuates Ca^{2+} influx in adult and developing brain tissue and antagonizes depolarization-evoked Ca^{2+} efflux (Kontro and Oja, 1988). Furthermore, intracellular swelling of neurons and glial cells due to activation of glutamate receptors (Saransaari and Oja, 1991) is also attenuated by the extracellularly released taurine (Walz and Allen, 1987).

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