Amino Acids (2000) 19: 509–526

Amino
Acids

Taurine and neural cell damage

Review Article

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Accepted January 31, 2000

Summary. The inhibitory amino acid taurine is an osmoregulator and neuromodulator, also exerting neuroprotective actions in neural tissue. We review now the involvement of taurine in neuron-damaging conditions, including hypoxia, hypoglycemia, ischemia, oxidative stress, and the presence of free radicals, metabolic poisons and an excess of ammonia. The brain concentration of taurine is increased in several models of ischemic injury in vivo. Cell-damaging conditions which perturb the oxidative metabolism needed for active transport across cell membranes generally reduce taurine uptake in vitro, immature brain tissue being more tolerant to the lack of oxygen. In ischemia nonsaturable diffusion increases considerably. Both basal and K^+-stimulated release of taurine in the hippocampus in vitro is markedly enhanced under cell-damaging conditions, ischemia, free radicals and metabolic poisons being the most potent. Hypoxia, hypoglycemia, ischemia, free radicals and oxidative stress also increase the initial basal release of taurine in cerebellar granule neurons, while the release is only moderately enhanced in hypoxia and ischemia in cerebral cortical astrocytes. The taurine release induced by ischemia is for the most part Ca^{2+}-independent, a Ca^{2+}-dependent mechanism being discernible only in hippocampal slices from developing mice. Moreover, a considerable portion of hippocampal taurine release in ischemia is mediated by the reversal of Na^+-dependent transporters. The enhanced release in adults may comprise a swelling-induced component through Cl^- channels, which is not discernible in developing mice. Excitotoxic concentrations of glutamate also potentiate taurine release in mouse hippocampal slices. The ability of ionotropic glutamate receptor agonists to evoke taurine release varies under different cell-damaging conditions, the N-methyl-D-aspartate-evoked release being clearly receptor-mediated in ischemia. Neurotoxic ammonia has been shown to provoke taurine release from different brain preparations, indicating that the ammonia-induced release may modify neuronal excitability in hyperammonic conditions. Taurine released simultane-

ously with an excess of excitatory amino acids in the hippocampus under ischemic and other neuron-damaging conditions may constitute an important protective mechanism against excitotoxicity, counteracting the harmful effects which lead to neuronal death. The release of taurine may prevent excitation from reaching neurotoxic levels.

Keywords: Amino acids – Taurine – Cell-damaging conditions – Ischemia – Brain

Introduction

Taurine

Taurine (2-aminoethanesulfonic acid) is one of the most abundant free amino acids in the central nervous system. In many mammals its concentration even exceeds that of glutamate during ontogenic development (Oja and Kontro, 1983a). This simple sulfonic acid has been thought to have a special role in immature brain tissue (Oja and Kontro, 1983a; Kontro and Oja, 1987a; Sturman, 1993). It is a vital nutrient for cats, and probably also for primates, being essential for the development and survival of neural cells (see Huxtable, 1992; Sturman, 1993). In kittens a dietary deficiency of taurine manifests itself in morphological degeneration of the retina and tapetum lucidum and in pathological alterations in the electroretinogram and visual evoked potentials in cats and monkeys (Sturman et al., 1985). In taurine-deficient kittens mitotic activity also persists and migration of granule cells from the external granule cell layer to the inner layers in the cerebellum is delayed (Sturman et al., 1985). These observations have given impetus to taurine supplementation of infant formulas derived from taurine-poor cow milk. On the other hand, taurine is known to act as an osmoregulator in marine animals (Simpson et al., 1959), and is thought to function in the same role in the brains of terrestrial species (Walz and Allen, 1987; Pasantes-Morales and Schousboe, 1997). Furthermore, taurine induces hyperpolarization and inhibits firing of central neurons. It has therefore come to be regarded as an inhibitory transmitter or more precisely a modulator of nervous activity (Oja et al., 1977; Oja and Kontro, 1983a; Huxtable, 1992; Saransaari and Oja, 1992).

Neural cell damage

Hypoxia, hypoglycemia, ischemia and free radical production cause neuronal cell damage and death. In ischemia, oxidative metabolism shifts to anaerobic glycolysis due to the lack of oxygen and glucose. The generation of high-energy phosphate reserves is then insufficient to maintain cellular ionic gradients and other metabolic processes. In oxidative metabolism biological systems tend to produce free radicals. Free radical levels and membrane lipid peroxidation may become abnormally high under certain conditions, including ischemia and ageing, and damage membrane structures in nerve cells (Haddad and Jiang, 1993; Hara et al., 1993). Free radicals are also thought to

be involved in certain neurological diseases (Halliwell, 1992; Bondy, 1995). The effects of ischemia and exposure to free radicals share many common features (Gilman et al., 1994).

High extracellular concentrations of excitatory amino acids are neurotoxic, and overstimulation of their receptors due to an increased release from intracellular stores contributes to neuronal death during cerebral ischemia (see Rothman and Olney, 1988; Szatkowski and Attwell, 1994). Excitatory amino acids are massively released from neural structures during hypoxia and ischemia both in vitro (Pellegrini-Giampietro et al., 1990; Collard and Menon-Johansson, 1993; O'Regan et al., 1995a,b) and in vivo (Benveniste et al., 1984, Hagberg et al., 1985; Globus et al., 1988). Moreover, the release of excitatory amino acids is in part a consequence of the action of oxygen-derived free radicals formed in hypoxic brain tissue (Pellegrini-Giampietro et al., 1988). Free radicals and excitatory amino acids thus cooperate in the genesis of ischemia-induced neuronal damage (Halliwell and Gutteridge, 1985; Pellegrini-Giampietro et al., 1990; Coyle and Puttfarcken, 1993). The activation of the N-methyl-D-aspartate (NMDA) class of glutamate receptors in particular increases the intracellular concentration of Ca^{2+} and triggers a long-lasting potentiation of NMDA-gated currents (Szatkovski and Attwell, 1994).

Neuroprotective effects of taurine

Taurine is known to protect neural cells from the excitotoxicity induced by excitatory amino acids (Fariello et al., 1982; French et al., 1986; Trenkner, 1990). It forestalls the harmful metabolic cascades evoked by ischemia and hypoxia (Schurr et al., 1987) and attenuates Ca^{2+} influx in ischemia (Lehmann et al., 1985). An endogenous taurine-containing dipeptide γ-L-glutamyltaurine also efficiently attenuates glutamate-agonist-evoked calcium fluxes in neurons (Varga et al., 1992). Taurine-containing neurons are fairly resistant to cerebral ischemia induced by the four-vessel occlusion (Matsumoto et al., 1991; Wu et al., 1994). Taurine protects cerebellar granule cells exposed to kainate without affecting the production of reactive oxygen species in these cells (Boldyrev et al., 1999).

Taurine has ameliorated epileptic symptoms in experimental animals and human patients (Kontro and Oja, 1983b). However, a perusal of the literature shows that only about one third of human patients clearly respond to taurine medication, as was also the case in our own patient series of intractable cases of epilepsy in children (Airaksinen et al., 1980). Taurine penetrates into the brain slowly (Oja et al., 1976), because the molecule is fairly lipophobic and the active uptake systems are not very effective (Lähdesmäki and Oja, 1973). On the other hand, an excess of taurine in plasma is readily excreted into urine (Chesney et al., 1985). The brain level is thus only marginally elevated after oral or parenteral administration of taurine. With this in mind we have endeavored to develop lipophilic taurine derivatives which could more readily penetrate brain tissue and act as antiepileptics. A few such derivatives appeared fairly effective in rodent seizure models (Lindén et al., 1983; Oja et al.,

1983), but taltrimide (2-phthalimidosulfon-N-isopropylamine), when subjected to clinical trials failed to ameliorate symptoms in intractable epileptic patients (Airaksinen et al., 1987). Like the parent compound, taurine, taltrimide affects GABAergic neurotransmission (Kontro and Oja, 1987c), which interaction may underlie its failure in clinical trials. Taltrimide potentiates basal taurine release in normoxia but not the ischemia-induced release in mouse hippocampal slices (Saransaari and Oja, 1999b). In our opinion there nevertheless remain unexplored possibilities of modifying the taurine molecule in a search for novel anticonvulsants and neuroprotectants.

The mechanisms of neuroprotective effects are not known but may be related, in addition to neuromodulation and osmoregulation, to the antioxidant and calcium ion regulatory actions of taurine. We review now the involvement of taurine in certain neuron-damaging conditions, including hypoxia, hypoglycemia and ischemia. Cell damage caused by oxidative stress, free radicals and metabolic poisons is also discussed, as well as the role of taurine in ammonia toxicity.

Taurine under different cell-damaging conditions

Taurine levels in vivo

The extracellular concentrations of taurine together with other amino acids have been measured by microdialysis in several animal models of ischemic injury in vivo. The levels have been found to be increased in the rat striatum (Uchiyama-Tsuyuki et al., 1994) and rabbit cerebral cortex (Matsumoto et al., 1996) after transient focal ischemia, in the rat cerebral cortex in the four-vessel occlusion model (Phillis et al., 1999), after aortic occlusion in the rabbit spinal cord (Simpson et al., 1990) and after forebrain ischemia in the hippocampus of both normal (Lekieffre et al., 1992) and spontaneously hypertensive rats (Ooboshi et al., 1995). In this latter experimental paradigm the ischemia-induced release of taurine was smaller in aged rats than in adults, contributing to the age-related vulnerability of hippocampal neurons to ischemia (Ooboshi et al., 1995). In a global model of brain ischemia taurine was seen to be accumulated in the rat auditory cortex and cerebrospinal fluid (Shimada et al., 1993). In anoxia, on the other hand, extracellular taurine in the striatum of newborn rats began to increase only after the anoxia-induced elevation of extracellular K^+ (Pérez-Pinzón et al., 1993). Hypoxia alone did not affect the hippocampal taurine level but markedly prolonged the increase in a rat model with controlled closed head injury followed by hypoxia (Katoh et al., 1997). A similar delayed release of taurine has also been noted under a number of experimental conditions in many brain preparations in vitro (see Saransaari and Oja, 1992). Furthermore, the taurine concentration in the rat piriform cortex rose during focal ischemia and remained elevated, though somewhat attenuated, throughout the subsequent reperfusion phase (Lo et al., 1998). The response to K^+ stimulation was significantly attenuated after this ischemia reperfusion. The long-lasting increase in extracellular taurine

after injury may be beneficial to damaged tissue, but not the attenuation of responses to K^+ stimulation during reperfusion.

Taurine uptake in vitro

Taurine possesses saturable, Na^+-dependent transport systems operating in neuronal and glial cell membranes and comprising both high- and low-affinity components (see Oja and Kontro, 1983a; Huxtable, 1992). Conditions which are known to cause neural cell damage affect taurine uptake in mouse cerebral cortical synaptosomal preparations (Saransaari and Oja, 1996). Metabolic poisons, hypoglycemia, hypoxia and ischemia all perturb the oxidative metabolism needed for active taurine transport across cell membranes. Short-term exposure to hypoxia or ischemia has proved to have no apparent effect on taurine uptake measured at a 10-μM concentration, but kinetic analyses revealed that nonsaturable diffusion nevertheless increased under ischemic conditions, the increase manifesting itself only at higher concentrations (Saransaari and Oja, 1996). Apparently there was greater leakage of taurine molecules into synaptosomes through partially disrupted membranes, though the operation of carriers was still almost intact. Only the maximal velocity of low-affinity uptake was increased, indicating that more transport sites were available or that the translational step was faster. However, long-lasting exposure to ischemia gradually reduced the uptake, the inhibition being more pronounced in the adult than in developing mice. The taurine uptake systems, which are more efficient in the immature than the mature cerebral cortex (Oja and Kontro, 1984), better tolerate perturbations of oxidative metabolism. This is in keeping with the observation that the immature brain is markedly resistant to both brief and prolonged periods of hypoxia (Nabetani and Okada, 1994). Oxidative stress and the experimental conditions inducing free radical production have been seen to affect taurine uptake only in adults. The transport systems were not affected by these insults in the immature brain (Saransaari and Oja, 1996).

Basal and K^+-stimulated taurine release in vitro

The basal and K^+-stimulated release of both endogenous and exogenous taurine have been modified by tissue-damaging experimental conditions in the hippocampi of developing, adult and ageing mouse (Saransaari and Oja, 1996, 1997a, 1998a). The basal release of [^{3}H]taurine from hippocampal slices from developing mice is markedly increased in the presence of 2,4-dinitrophenol (DNP). Hypoglycemia, ischemia and media inducing free radical production were likewise fairly effective, and NaCN and hypoxia caused small increases (Fig. 1). In hippocampal slices from young adult mice the basal release of taurine was enhanced by the same experimental conditions (Fig. 2), ischemia being in this case the most effective of them. Free radicals, NaCN and DNP were now almost equipotent, and hypoxia and hypoglycemia were also fairly effective. Oxidative stress does not affect taurine release in mouse

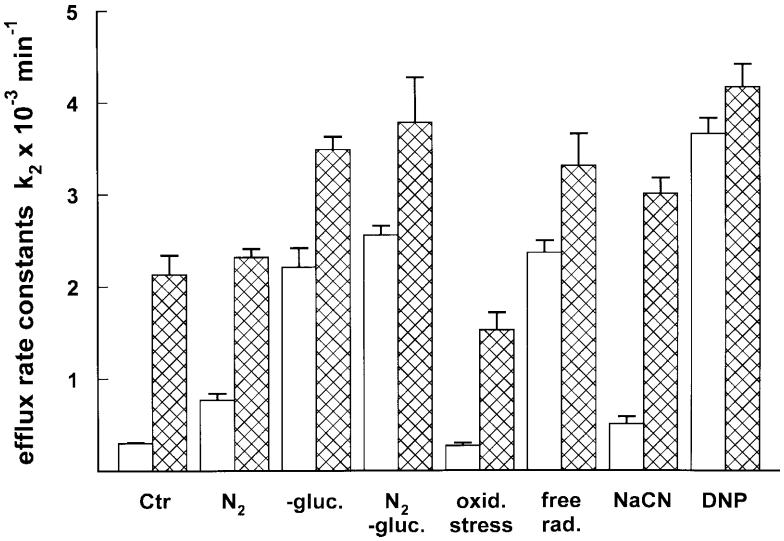

Fig. 1. Taurine release from hippocampal slices from 7-day-old mice under different cell-damaging conditions. The freely floating slices, preloaded for 30 min with 10 μM [^{3}H]taurine, were superfused for 50 min with glucose-containing or glucose-free (hypoglycemia and ischemia) Krebs-Ringer media continuously bubbled with O_2 or N_2 (hypoxia and ischemia). Oxidative stress was induced by 7.5 μM $FeSO_4$ and free radical production achieved by exposure to 0.01% H_2O_2. The concentration of NaCN and 2,4-dinitrophenol was 1 mM. From 30 min onwards the medium in every second experiment was supplemented with 50 mM K^+ (potassium stimulation). The results are mean efflux rate constants (+SEM) k_2 (34–50 min) of 4–8 independent experiments. Basal unstimulated release (open bars) and K^+-stimulated release (cross-hatched bars). Basal unstimulated release was significantly ($P < 0.01$) increased in all other cases except in oxidative stress. K^+ stimulation significantly ($P < 0.01$) enhanced the release in all other cases except in the presence of 1 mM DNP. The graph is composed from the results in Saransaari and Oja (1997d,1999c) and from our unpublished results

hippocampal slices (Saransaari and Oja, 1997a, 1998a), while in cultured retinal cells oxidative stress, hypoxia and ischemia have increased release in the presence of Ca^{2+} (Rego et al., 1996).

In hippocampal slices from adult mice, stimulation by 50 mM K^+ failed to evoke any significant potentiation of taurine release under hypoglycemic and hypoxic conditions, in free radical-containing medium and in the presence of NaCN, but enhanced the release in oxidative stress (Fig. 2). In ischemia and in the presence of DNP, taurine release was even diminished when the slices were exposed to medium with a high K^+ concentration. In the developing hippocampus, the enhancement of release by K^+ stimulation was generally preserved under cell-damaging conditions (Fig. 1). The only exception was observed in the presence of DNP in superfusion medium, in which case the release was markedly diminished. The increase in taurine release under ischemic conditions was reversible after the introduction of control aerobic conditions in both age groups (Saransaari and Oja, 1997a). On the other hand, when the slices were poisoned with DNP a gradual recovery was seen after its

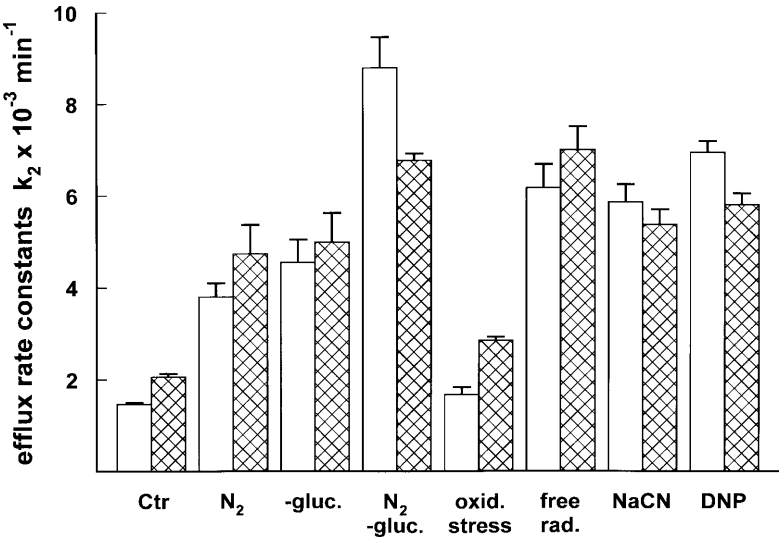

Fig. 2. Taurine release from hippocampal slices from 3-month-old mice under different cell-damaging conditions. The experiments made and the symbols are the same as in Fig. 1. The results are mean efflux rate constants (+SEM) k_2 (34–50 min) of 4–8 independent experiments. Basal unstimulated release was significantly ($P < 0.01$) increased in all other cases except in oxidative stress. K^+ stimulation significantly ($P < 0.01$) enhanced the release in control experiments and in oxidative stress and diminished it in ischemia and in the presence of DNP. The graph is composed from the results in Saransaari and Oja (1997d, 1999c) and from our unpublished results

omission from superfusion medium in slices from immature mice, but not in those from adults. The release of endogenous taurine has been doubled in hypoxia and tripled in ischemia in adult hippocampal slices, but K^+ stimulation is abolished (Saransaari and Oja, 1998a). In the immature hippocampus the increase in taurine release was 10-fold in hypoxia and 30-fold in ischemia, K^+-stimulation being still partly preserved (Saransaari and Oja, 1998a).

In glutamatergic cerebellar granule cells hypoxia and ischemia have produced an initial increase in the basal release of taurine when compared to normoxia, but the response to K^+ has been diminished (Saransaari and Oja, 1999d). Hypoglycemia, oxidative stress and free radicals have enhanced taurine release and subsequent K^+ treatment causes a correspondingly greater stimulation. The magnitude of K^+ stimulation is identical in hypoxia and in controls, whereas in ischemia the response is somewhat attenuated (Fig. 3A). A common feature of taurine release in all the above conditions in granule cells is a slow response to K^+ stimulus, particularly to that of veratridine (Saransaari and Oja, 1999d). Maximal release has occurred invariably only after cessation of stimuli. On the other hand, in cultured cerebral cortical astrocytes the basal release of taurine is only moderately enhanced in hypoxia and ischemia, whereas the potentiation by free radicals is marked (Saransaari and Oja, 1999c). The small basal release from astrocytes signifies that taurine release from brain tissue in ischemia may originate from neurons rather than from glial cells. Moreover, the release evoked by K^+ is greater in hypoxia and

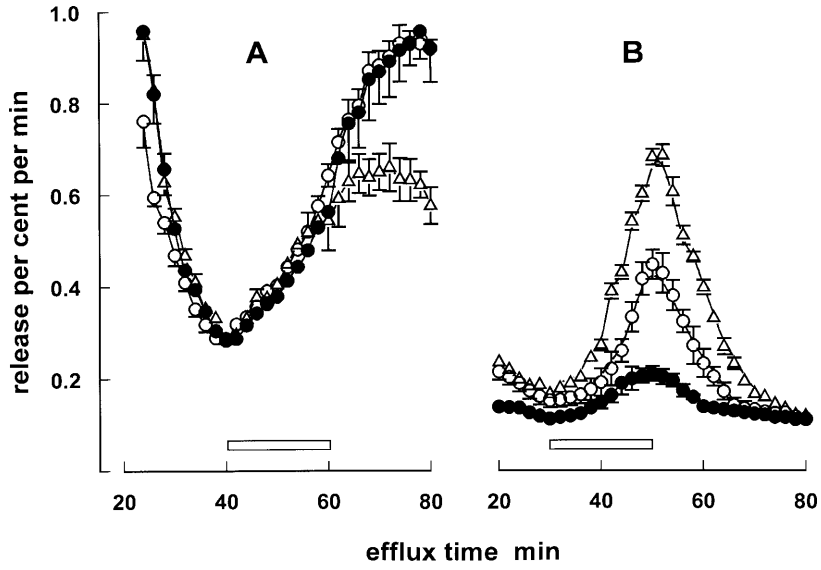

Fig. 3. Time-course of taurine release from cultured cerebellar granule cells (**A**) and cerebral cortical astrocytes (**B**). The cells were preloaded with 10μM [^{3}H]taurine in Krebs-Ringer-Hepes medium and the release of radioactivity was then monitored by changes of non-radioactive incubation medium at 2-min intervals. The medium was supplemented with 50 mM K^+ from 40 to 60 min (granule cells) and from 30 to 50 min (astrocytes) as indicated by the bars. Control (normoxia) (-●-), hypoxia (-○-) and ischemia (-△-). Hypoxic and ischemic conditions were generated as described in the legend to Fig. 1. The results are mean values of 4–6 independent experiments. SEM is shown if it exceeds the size of symbols. The graphs are composed from the data in Saransaari and Oja (1999a,b)

ischemia than in normoxia, with a relatively slow time-course (Fig. 3B). K^+ stimulation has also always evoked less taurine release from astrocytes than from granule neurons (Saransaari and Oja, 1999c,d). The enhanced release of inhibitory taurine from astrocytes in ischemia may be beneficial to surrounding neurons, since it outlasts the initial stimulus and counteracts impending hyperexcitation.

Mechanisms of ischemia-induced taurine release

General mechanisms

The properties of ischemia-induced release of neurotransmitters have been studied mainly with excitatory amino acids. Only the present authors have attempted to analyze the mechanisms of ischemia-induced taurine release. The increased release is apparently mediated by the same systems which are involved with aspartate and glutamate, multiple mechanisms being operative. Taurine release in ischemia may thus be enhanced by means of several mechanisms, including Ca^{2+}-dependent exocytotic release from nerve terminals, reversal of the functions of Na^+-dependent membrane transporters and facilitation of diffusion. Moreover, it has been suggested that the enhanced release of excitatory amino acids in ischemia may stem from membrane permeability

changes elicited by the activation of phospholipases by elevated intracellular Ca^{2+} (O'Regan et al., 1995a). Taurine efflux may also be a consequence of a regulatory volume decrease possibly mediated by ion channels and triggered as a response to ischemia-induced cell swelling.

Ca^{2+}-dependency

In normoxia taurine release has been seen to be more Ca^{2+}-dependent in the immature than the mature hippocampus (Saransaari and Oja, 1997a, 1998a,b). The release of both exogenous and endogenous taurine in hypoxia, hypoglycemia, ischemia, oxidative stress and in the presence of free radicals in the developing and adult hippocampus has been in all cases partially Ca^{2+}-dependent (Saransaari and Oja, 1997a, 1998a). In ischemia, the major part of release has been Ca^{2+}-independent in the adult and aged hippocampus (Saransaari and Oja, 1997a), whereas both basal and K^+-stimulated releases in the developing hippocampus have been attenuated in the absence of Ca^{2+} which indicates the involvement of Ca^{2+}-dependent processes (Saransaari and Oja, 1999a). On the other hand, the Ca^{2+} channel blocker nimodipine has no effect on the release in normoxia or ischemia in both the adult and developing hippocampus (Saransaari and Oja, 1998b, 1999a), which would imply that the L-type of voltage-dependent Ca^{2+} channels does not participate in the release.

In cultured retinal cells taurine release has increased in hypoxia and ischemia mainly by a Ca^{2+}-independent mechanism, while release in oxidative stress has required the presence of Ca^{2+} (Rego et al., 1996). Even though Ca^{2+}-dependent processes may be involved in ischemia-induced taurine release, the release could also result from excitotoxicity-induced cellular swelling under cell-damaging conditions. Both K^+ depolarization (Oja and Saransaari, 1992) and exposure to glutamate receptor agonists (Saransaari and Oja, 1991) have induced swelling-associated release of taurine in brain slices. The Ca^{2+}-dependent exocytosis of synaptic vesicles may thus play a minor role in the ischemia-evoked release in the immature hippocampus. Depolarization-induced release probably contributes to the initial release, but this is limited by the rapid inactivation and desensitization of both voltage- and glutamate-receptor-gated Ca^{2+} channels (Mody and MacDonald, 1995) and by the dependency of exocytotic release on adequate levels of ATP (Sánchez-Prieto et al., 1987). Furthermore, ischemia has been shown to initiate an initial exocytotic release of glutamate followed by a nonexocytotic release from cultured cerebellar granule cells (Pocock and Nicholls, 1998).

Na^+ effects

Both basal and K^+-stimulated hippocampal releases of taurine are markedly enhanced by Na^+ deficiency in normoxia, as demonstrated in mouse cerebral cortical and hippocampal slices (Kontro and Oja, 1987a,b; Oja and Kontro, 1987; Saransaari and Oja, 1998c). Na^+-free medium is known to diminish the K^+ content of the slices (Korpi and Oja, 1983) due to inhibition of Na^+, K^+-ATPase. In agreement with this, ouabain generally greatly stimulates the

basal release of taurine (Kontro and Oja, 1987a,b). This bespeaks the involvement of Na^+-dependent taurine transporters operating outwards. Indeed, developing and adult brain tissue possesses a saturable, Na^+-requiring transport system for taurine at neuronal and glial cell membranes, comprising both high- and low-affinity components (Oja and Kontro, 1983a; Huxtable, 1992), which could exhibit this kind of behavior. When the Na^+ gradient is dissipated, the preferred direction of transport changes from inward (uptake) to outward (release). Such a Ca^{2+}-independent release for glutamate has been assumed to be activated under certain pathological conditions, e.g., in anoxia (Sánchez-Prieto and Gonzales, 1988), but it appears also to operate for taurine in normoxia.

In ischemia, neurons are suddenly depolarized, being accompanied by a massive increase in the extracellular K^+ concentration and a decrease in extracellular Na^+ levels (Somjen et al., 1990). The reduction in ischemia-induced taurine release in Na^+-free media could to some extent result from the slow depolarization of cells in the total absence of extracellular Na^+ (Saransaari and Oja, 1998b). In addition to intracellular Na^+ ions, brain slices also lose intracellular K^+ in Na^+-free media (Korpi and Oja, 1983). Under these experimental conditions the K^+-evoked depolarization, riding on the ischemia-induced depolarizations, fails to enhance taurine release, even though the absence of extracellular Na^+ should have potentiated taurine release by reversal of the transporters (Saransaari and Oja, 1998b; 1999a). In Na^+-free medium K^+ ions may even partially adopt the role of Na^+ in promoting the function of transporters, since taurine release from brain slices is reduced when an excess of K^+ ions is added to the incubation medium (Korpi and Oja, 1983). In addition to this, the involvement of transporters in taurine release has been confirmed using the structural analogues hypotaurine and β-alanine, which potentiate taurine release by trans-stimulation in normoxia (Saransaari and Oja, 1998b; 1999a). Under Na^+-free conditions this stimulation was not discernible, the carriers not operating without Na^+. In ischemia, the significant potentiation of taurine release by β-alanine and hypotaurine constitutes further evidence that the heteroexchange also functions under ischemic conditions in the presence of Na^+. In Na^+-deficient medium in ischemia stimulation is absent. These results clearly show a substantial part of Ca^{2+}-independent taurine release in ischemia to be mediated by Na^+-dependent transport in the hippocampus. In keeping with this, taurine transporters in the mouse cerebral cortex remain operative in ischemia, though nonsaturable diffusion is greatly increased (Saransaari and Oja, 1996). Similarly, the release of glutamate (Roettger and Lipton, 1996) and GABA (Saransaari and Oja, 1997b) during ischemia has been shown to occur largely via reversal of the Na^+-dependent transport systems.

Involvement of ion channels

Attenuation of ischemia-evoked amino acid release by ion channel blockers would be consistent with the surmise that they exert their effects by prevent-

ing the movement of amino acids through swelling-activated anion channels as a part of the regulatory volume decrease (Pasantes-Morales, 1996; Strange et al., 1996). In this process swollen cells attempt to regain their normal volume by releasing osmolytes, including taurine. The swelling-induced increase in taurine release has been demonstrated to be mediated by simple diffusion without carrier involvement (Sánchez-Olea et al., 1991, 1993). Moreover, diffusion of other amino acids, including aspartate and glutamate, through an anion channel is thought to be partially responsible for the elevated levels of excitotoxic amino acids during ischemia (Phillis et al., 1997). The chloride channel inhibitors 4-acetamido-4-isothiocyanostilbene-2,2′-disulfonic acid (SITS) and 5-nitro-2-phenylpropylaminobenzoic acid (NPPB) have been found to reduce taurine release in vivo in normoxia and after four-vessel occlusion in the rat cerebral cortex (Phillis et al., 1997). Moreover, SITS and also diisothiocyanostilbene-2,2′-disulfonate (DITS) reduce only the K^+-stimulated taurine release under normal conditions in the developing hippocampus in vitro (Saransaari and Oja, 1999a), indicating that this release may occur through anion channels, though these channels may not be involved in the ischemia-induced release. This differs from the situation in the adult hippocampus, where a part of the enhanced taurine release in ischemia has been shown to occur through these channels (Saransaari and Oja 1998c). The involvement of K^+ and Na^+ channels in ischemic taurine release is also unlikely, since the corresponding channel blockers aminopyridine and amiloride have been without any effect (Saransaari and Oja, 1998b, 1999a, 2000).

Effects of membrane damage

An activation of membrane phospholipases upon damage to plasma membranes has been held responsible for a substantial fraction of the ischemia-induced release of excitatory amino acids (O'Regan et al., 1995b). Phospholipase inhibitors have reduced the ischemia-elicited release of glutamate and aspartate, while exogenously applied phospholipases enhance their efflux (O'Regan et al., 1995a,b; Phillis and O'Regan, 1996). Membrane disruption thus allows diffusion of compounds present intracellularly at high concentrations down their concentration gradient into the extracellular space. Phospholipase inhibitors have had no reducing effects on taurine release in hippocampal slices from both developing and adult mice (Saransaari and Oja, 1998b, 1999a). Moreover, the involvement of tyrosine phosphorylation and protein kinase C in the ischemia-induced release of taurine is unlikely in view of the absence of any effects of the corresponding enzyme inhibitors.

Excitotoxic damage

Excitotoxic conditions induced by high concentrations of glutamate have markedly potentiated hippocampal taurine release in both developing and adult mice, but the release is not significantly further enhanced in ischemia (Saransaari and Oja, 1998b, 1999a). The releasable pool of taurine is ap-

parently limited, in spite of its high tissue concentration in the developing hippocampus in particular (Saransaari and Oja, 1998a). On the other hand, the ionotropic glutamate receptor agonists NMDA, kainate and 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) have concentration-dependently potentiated taurine release in the developing, adult and ageing mouse hippocampus. Stimulations have been markedly greater in the immature than in the adult or ageing hippocampus (Saransaari and Oja, 1997c). The NMDA and AMPA receptors have proved to be involved in taurine release throughout the whole life-span of mice, while the kainate-receptor mediated release does not appear to function in adults. The ability of ionotropic glutamate agonists to evoke taurine release varies under different cell-damaging conditions (Saransaari and Oja, 1997d). In adults, glutamate agonists evoke release only in hypoxia and oxidative stress. The glutamate-receptor-stimulated release is generally operative in the immature hippocampus, except in the presence of DNP and free radicals, since they alone maximally potentiate the release. Furthermore, taurine release is greatly potentiated by exposure to media producing free radicals in both the mature and the immature hippocampus. The glutamate agonists then fail to evoke any additional release. Activation of the three ionotropic glutamate receptors can enhance taurine release in the developing hippocampus in hypoxia and oxidative stress and upon metabolic blockade by NaCN. In ischemia, the NMDA-evoked release has been shown to be not receptor-mediated, but both NMDA and kainate receptors induce taurine release in hypoglycemia (Saransaari and Oja, 1997d).

It has been speculated that the NMDA receptors may be the responsible mediators of ischemic brain damage and other excitotoxic syndromes in the immature brain (see Olney, 1993). This may explain the extreme sensitivity of the immature brain to excitotoxicity. Taurine released simultaneously with an excess of excitatory amino acids in the hippocampus may constitute an important protective mechanism against excitotoxicity, counteracting the harmful effects which lead to neuronal death. Release of this inhibitory amino acid may prevent excitation from reaching neurotoxic levels. On the other hand, the mammalian neonate is much more resistant to hypoxia than the adult (Vanucci, 1990). One reason for this phenomenon may be the high levels of taurine in young animals (Schurr and Rigor, 1987). Taurine enhances Cl^- conductance, inducing hyperpolarization and reducing cell excitability (Oja et al., 1990). It also attenuates Ca^{2+} influx and antagonizes depolarization-evoked Ca^{2+} efflux in the developing brain (Kontro and Oja, 1988). Moreover, taurine inhibits the cellular Ca^{2+} uptake elicited by NMDA (Lehmann et al., 1984) and preserves the integrity of neurons exposed to kainate (Fariello et al., 1982). The elevated extracellular levels of taurine would thus appear to contribute to the maintenance of homeostasis in the hippocampus upon impending hyperexcitation.

Ammonia toxicity

Ammonia is a neurotoxin which provokes a variety of neurological symptoms. At high doses, it has a depolarizing action on neuronal membranes (Iles and

Jack, 1980), causing epileptiform seizures and eventual death (Marcaida et al., 1992). At low doses, it exhibits hyperpolarizing effects (Szerb and Butterworth, 1992). The neurophysiological effects of ammonia probably originate from its influences on central excitatory and/or inhibitory transmitter mechanisms, as recently reviewed by Albrecht (1998). A possible role for excitatory amino acids has been suggested, implicating the activation of NMDA receptors (Hermenegildo et al., 1996). Ammonium chloride at concentrations measured during acute hyperammonemia has stimulated taurine release in cultured rabbit Müller cells (Faff-Michalak et al.,1994; Faff et al., 1997), rat cortical astrocytes (Albrecht et al., 1994) and cultured rat cerebellar astrocytes and granule cells (Wysmyk et al., 1994). The ammonia-induced taurine release in rabbit Müller cells has been shown to be mediated by an intracellular accumulation of cAMP (Faff et al., 1996). Moreover, hepatic encephalopathy induced by the hepatotoxin thioacetamide has elevated taurine concentrations in the basal ganglia and cerebral cortex (Hilgier et al., 1996). The K^+-stimulated release of taurine is also enhanced in the striatum of rats treated with thioacetamide (Wysmyk et al., 1991). High concentrations of ammonia evoke release in striatal slices prepared from them. Ammonia-induced taurine efflux from rat cerebrocortical minislices has been accompanied by an increase in cell volume, but the underlying mechanism was not inferred to be a simple cell volume regulatory response normally discernible in hypoosmotic stress (Zielińska et al., 1999). These results indicate that the ammonia-induced taurine release may also modify neuronal excitability accompanying hyperammonic conditions. The taurine released could counteract the ammonia-induced excitation of neurons in acute hyperammonemia or augment neural inhibition associated with chronic hyperammonemia (Albrecht, 1998).

Acknowlegements

The technical assistance of Mrs Sari Luokkala and the financial support of the Medical Research Fund of Tampere University Hospital and the Academy of Finland are gratefully acknowledged.

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Received January 25, 2000