Transcortical Alterations in Na⁺-K⁺ ATPase and Microtubule-Associated Proteins Immunoreactivity in the Rat Cortical Atrophy Model Induced by Hypoxic Ischemia

Jun-Gyo Suh, Sung-Jin An, Jae-Bong Park, Zae-Young Ryoo, Jeong Woong Lee, Yang-Seok Oh, Moo Ho Won and Tae-Cheon Kang

Department of Medical Genetics & Experimental Animal Center, 2Anatomy, and 3Biochemistry, College of Medicine, Hallym University Chunchon 200-702, South Korea; 4Laboratory Animal Center, Institute of Medical Science, Catholic Medical College, Seoul 137-701, South Korea

SUMMARY

To identify the chronological transcortical change in the contralateral hemisphere following ischemic insults, we investigated the changes in microtubule associated protein (MAP) and Na⁺-K⁺ ATPase expressions in the peri-infarct zone and contralateral hemisphere, including the hippocampus. Two days after hypoxic ischemia, Na⁺-K⁺ ATPase immunoreactivity was significantly enhanced in the contralateral cortex and was maintained up to 7 days after ischemia, whereas Na⁺-K⁺ ATPase immunoreactivity in the peri- and infarct zones was unaffected by hypoxic ischemia. In contrast, 2 to 7 days after ischemia, MAP1A and MAP2 immunoreactivity in the ipsi- and contralateral cortex significantly decreased, whereas in layer V, MAP1 immunoreactivity obviously accumulated in the neurons and their processes. In the hippocampus, 2 days after insults both MAP1A and MAP2 immunoreactivity was significantly reduced within the ipsi- and contralateral hippocampus. In the contralateral hippocampus, however, the distribution of MAP2 immunoreactivity recovered to the sham level 7 days after ischemia, whereas MAP1A immunoreactive axons remained 2 months after ischemia. The results suggest that the unilateral elevation of Na⁺-K⁺ ATPase immunoreactivity reflects elevated neuronal activity. In addition, this asymmetric hyperexcitability might play an important role in the recovery or the reorganization of the brain, accompanied by transcortical changes in MAPs expression.

KEYWORDS

transcortical change, diaschisis, rat, hippocampus, microtubule associated protein, Na⁺-K⁺ ATPase

INTRODUCTION

Neurodegenerative diseases evoke certain morphological alterations at a lesion site; e.g., dendritic sprouting and axonal degeneration. Moreover, neuronal responses after injury can play an important role in the maintenance or reconstruction of brain functionality. In fact, such
alterations increase behavioral recovery after various cortical lesions including cortical ablations, contusions, and focal ischemia in animals and after stroke in humans. Microtubule-associated proteins (MAPs) are generally used as morphological markers of neuronal plasticity because these proteins are abundant in both axons and dendrites, where they are thought to be involved in intracellular transport functions (Grafstein & Forman, 1980). MAPs are also responsible for the maintenance of mature neuronal morphology and for the initiation and stabilization of new fibers and synaptic contacts (Tucker et al., 1989; Hirokawa et al., 1996; Marsden et al., 1996).

In addition, one of the earliest events after brain damage, including cerebral ischemia, is a rapid decline in the activity of energy dependent sodium-potassium adenosine triphosphatase (Na+-K+ ATPase) (Lees, 1991). Several investigators (Stys et al., 1992; Tasker et al., 1992) have examined the role of tetrodotoxin-sensitive ion channels in hypoxic-ischemic neuronal damage and concluded that Na+ influx is an important initiating event leading to neuronal damage. The truth is that the state of membrane failure of the Na+-K+ transport mechanism leads to the net leakage of these ions, and to the accumulation of K+ in the extracellular space. Thus, at this point the cells take up Na+ and Cl−, with osmotically obligated water. These events lead to rapid edema, resulting in cell death in the ischemic brain (Astrup, 1982; Siesjo, 1988).

On the other hand, one hypothesis is that cortical damage is accompanied by secondary changes in the contralateral brain regions, which contributes to initial non-specific behavioral depression. These remote effects, referred to as ‘disachisis’, are most commonly observed several hours after an insult and recover within the following month (Reinecke et al., 1999; Lagreze et al., 1987). With respect to etiology, brain edema or reactive plasticity causes the remote changes (Witte et al., 2000). The functional importance of such alterations is presumably a prerequisite for restitution (Kotila & Waltimo, 1992; So et al., 1996). Unfortunately, few systemic studies have been done on the chronological transcortical change in the peri-infarct region or in the contralateral hemisphere following ischemic insults. In the present study, therefore, we investigated changes of both MAPs and Na+-K+ ATPase expressions to identify the chronic patterns of regional specific alterations in the peri-infarct zone and its contralateral hemisphere, including the hippocampus, following ischemic insults.

**EXPERIMENTAL**

**Hypoxic ischemia**

The animals used in this study were the progeny of male Sprague-Dawley rats (aged 4 wk) obtained from the Experimental Animal Center, Hallym University, Chunchon, South Korea. The animals were provided with a commercial diet and water *ad libitum* under controlled temperature, humidity, and lighting conditions (22 ± 4 °C, 55 ± 5% and a 12:12 light/dark cycle). The procedures involving animals and their care were conducted in conformity with the institutional guidelines that are in compliance with international laws and policies (NIH Guide for the Care and Use of Laboratory Animals, NIH Publication No. 85-23, 1985).

Focal hypoxic ischemia was induced using the procedure of Levine (1960) as modified by Rice et al. (1981). Briefly, the right carotid artery of animals was ligated, after which the animals were exposed for 1.5 h to hypoxic conditions (8% O2, 92% N2O, 30 °C temperature, 60% humidity). Two control groups were used for this experiment; a sham-operated group, which was subjected to the same surgical procedures but without hypoxia-
ischemia (n = 5), and the other control group was exposed to the hypoxic condition only (n = 5).

**Preparation of animals and tissue**

After a period of 2 days, 7 days, and 2 months (n = 10, respectively), animals were perfused transcardially with phosphate-buffered saline (PBS), followed by 4% paraformaldehyde in 0.1 M PB (pH 7.4), after deep anesthesia (i.p.) had been induced with Ketamine. The brains were removed and postfixed for 4 h in the same fixative. The brain tissues were cryoprotected by infiltration with 30% sucrose overnight. Thereafter, the tissues were frozen and sectioned with a cryostat at 30 μm, and consecutive sections were collected in 6-well plates containing PBS.

**Immunohistochemistry**

The sections were first incubated for 30 min with 3% bovine serum albumin in PBS at room temperature. Some sections were then incubated overnight in mouse anti-MAP1A (Chemicon, USA), MAP2 (Boehringer Mannheim, USA), or anti-Na⁺-K⁺ ATPase α1 subunit antibodies (a6F, Developmental Studies Hybridoma Bank, USA), diluted 1:200 to 1:400 in PBS containing 0.3% triton X-100 and 2% normal horse serum at room temperature. The sections were washed with PBS three times for 10 min each, incubated sequentially, in horse anti-goat IgG (Vector, USA) and streptavidin (Vector, USA), diluted 1:200 in the same solution used for the primary antiserum. Between the incubations, the tissues were washed with PBS three times for 10 min each. The sections were visualized with 3,3'-diaminobenzidine (DAB) in 0.1 M Tris buffer and mounted on gelatin-coated slides. The immunoreactivity was observed under the Axioscope microscope (Carl Zeiss, Germany). To establish the specificity of the immunostaining, a negative control test was carried out with pre-immune serum instead of the primary antibody. The control for immunohistochemistry resulted in the absence of immunoreactivity in any structure.

**RESULTS**

In the present study, preparations from the control animals did not show any morphological change in the brain tissue (data not shown). The operated animals had ipsilaterally extensive damage to the cortex, including the hippocampus, similar to that described previously by Romijn et al. (1992, 1993), although the contralateral hemisphere had no lesions.

**Na⁺-K⁺ ATPase immunoreactivity**

Na⁺-K⁺ ATPase immunoreactivity in the cortices of control animals showed symmetrical distribution, and this pattern was similarly observed in the hippocampus (Fig. 1A). 2 days after hypoxic ischemia, Na⁺-K⁺ ATPase immunoreactivity was significantly enhanced in the contralateral cerebral cortex, whereas Na⁺-K⁺ ATPase immunoreactivity in the peri- and infarct zones was unaltered. In contrast to the cerebral cortex, Na⁺-K⁺ ATPase immunoreactivity was increased in the lentiform nucleus ipsilateral to the infarct lesion (Fig. 1B). Seven days after hypoxic ischemia, elevated Na⁺-K⁺ ATPase immunoreactivity was maintained in the contralateral cortex, and its immunoreactivity was unchanged in the peri-infarct zone. In the infarct zone of the cerebral cortex, however, non-specific Na⁺-K⁺ ATPase immunoreactivity occurred because this region was degenerated (Fig. 1C). Two months after ischemic insult, the Na⁺-K⁺ ATPase immunoreactivity was unchanged in the peri-infarct zone.

Na⁺-K⁺ ATPase immunoreactivity in the contralateral cortex, however, was significantly
Fig. 1: Na⁺-K⁺ ATPase immunoreactivity in rat cortices following hypoxic ischemia. In the control animal, a symmetrical distribution of Na⁺-K⁺ ATPase immunoreactivity is observed in the brain (A). Two days after hypoxic ischemia (B), Na⁺-K⁺ ATPase immunoreactivity is significantly enhanced in the contralateral cerebral cortex (arrows), whereas Na⁺-K⁺ ATPase immunoreactivity in peri- and infarct zones is unaltered (open arrows). Seven days after hypoxic ischemia (C), elevated Na⁺-K⁺ ATPase immunoreactivity in the contralateral cortex is maintained (arrows), and its immunoreactivity is unchanged in the peri-infarct zone (open arrow). Two months after ischemic insult (D), the Na⁺-K⁺ ATPase immunoreactivity is unchanged in the peri-infarct zone (open arrow). Na⁺-K⁺ ATPase immunoreactivity in the contralateral cortex, however, is significantly decreased (arrow). Bar = 1,500 μm.

decreased as compared with that observed 7 days after hypoxic ischemia. Both the infarct zone and the ipsilateral hippocampus had completely disappeared at this stage, due to atrophy of the ischemic lesion (Fig. 1D).

MAP1A immunoreactivity

Unlike Na⁺-K⁺ ATPase immunoreactivity, MAP1A immunoreactivity was simultaneously altered in the cerebral cortex and the hippocampus. Compared with the sham cortex (Figs. 2A, 2B), 2 days after ischemia, MAP1A immunoreactivity significantly decreased, but in layer V, MAP1A after ischemia, accumulated MAP1A immunoreactive neurons disappeared from the peri-infarct zone and the contralateral cortex, but immunoreactivity was maintained in axons (Figs. 2E, 2F).

MAP1A immunoreactivity also decreased in the hippocampus compared with the sham (Figs. 3A, 3B). Like in the cerebral cortex, MAP1A immunoreactivity accumulated in some hilar neurons in both sides of the hippocampus 2 days after insult and was maintained 7 days after hypoxic ischemia (Figs. 3C, 3D). Interestingly, MAP1A immunoreactive axons remained in the contralateral hippocampus 2 months after ischemia (Figs. 3E, 3F).
Fig. 2: MAP1A immunoreactivity in the rat cerebral cortex. In the sham cortex, MAP1A immunoreactivity is similarly detected both in contralateral (A) and ipsilateral (B) cortices to infarct region. Two days after ischemia (C and D), MAP1A immunoreactivity in layer V is had obviously accumulated in neurons and their axons, although MAP1A immunoreactivity was significantly decreased (arrows indicate layer VI). Two months after ischemia, accumulated MAP1A immunoreactive neurons disappeared from the contralateral cortex (E) and the peri-infarct zone (F), in contrast, MAP1A immunoreactivity is maintained in axons. Bar = 100 μm.
Fig. 3: MAP1A immunoreactivity in the rat hippocampus. In the sham cortex, MAP1A immunoreactivity is similarly detected both in the contralateral (A) and ipsilateral (B) hippocampi to infarct region. Two days after insults (C and D), MAP1A immunoreactivity had accumulated in some hilar neurons in both sides of the hippocampus (arrows). Two months after ischemia, MAP1A immunoreactive axons (arrows) remained in the contralateral hippocampus (E and F). Bar = 100 μm (A–E); 50 μm (F).
MAP2 immunoreactivity

Contrary to MAP1A immunoreactivity, the distributions of MAP2 immunoreactivity was simultaneously altered in the cerebral cortex, but not in the hippocampus. Compared with the sham cortex (Figs. 4A, 4B), MAP2 immunoreactivity significantly decreased, particularly in layers IV and V, thus MAP2 immunoreactive processes were scattered in these layers. In layer VI, however, MAP2 immunoreactivity was unaltered (Figs. 4C, 4D). Similar MAP2 immunoreactive patterns were detected in the peri-infarct zone and in the contralateral cortex until 7 days after hypoxic ischemia. Two months after ischemia, MAP2 immunoreactivity in these regions recovered to the sham levels (Figs. 4E, 4F).

Compared with the sham (Figs. 5A, 5B), 2 days after insult, MAP2 immunoreactivity in the contralateral hippocampus significantly decreased. In the ipsilateral hippocampus, MAP2 immunoreactivity in the dentate hilar region also declined (Figs. 5C, 5D). Seven days after hypoxic ischemia, in the contralateral hippocampus, the immunodensity and the distribution of MAP2 immunoreactivity recovered to the sham level. In the ipsilateral hippocampus, however, MAP2 immunoreactivity was detected in the sprouting dendrites of the remaining hilar neurons and in the granule cells (Figs. 5E, 5F).

DISCUSSION

Within a few hours after ischemia, a progressive net uptake of water from the blood-brain barrier results in an increase of total tissue water (Huang et al., 1999; Hatashita et al., 1990). This brain edema is remarkably prolonged after 24 to 72 h (Forsting et al., 1994; Rosenberg, 1999), during which it produces massive secondary damage by compressing the contralateral brain and other remote brain areas and induces an associated secondary ischemia caused by the compression of the vessels. This secondary contralateral edema returns almost to baseline 2 weeks after the injury (for review see Witte et al., 2000).

In the present study, 2 days after hypoxic ischemia, ATPase Na⁺-K⁺ immunoreactivity was significantly enhanced in the contralateral cortex and was maintained for 7 days after ischemia, whereas Na⁺-K⁺ ATPase immunoreactivity in the peri- and infarct zones was unaltered. The results of this experiment indicate that the up-regulation of Na⁺-K⁺ ATPase immunoreactivity may play an important role in the recovery of the contralateral cortical lesion because Na⁺-K⁺ ATPase maintains neuronal volume by regulating osmolarity (Astrup, 1982; Siesjo, 1988). Therefore, this unilateral (contralateral) elevation of Na⁺-K⁺ ATPase immunoreactivity may be a compensatory response that prevents cytotoxic edema. The asymmetric increase of Na⁺-K⁺ ATPase immunoreactivity also suggests that neuronal activity in the contralateral cortex may be elevated because hyperexcitability in the contralateral cortex is induced by the decreased GABAergic inhibition (Buchkremer-Ratzmann & Witte, 1996; Redecker et al., 2000; Witte et al., 2000).

MAPs are a family of cytoskeletal proteins that are responsible for maintaining mature neuronal morphology and for initiating and stabilizing new fibers and intracellular transport functions (Grafstein & Forman, 1980; Solomon, 1980; Tucker et al., 1989). Ischemic lesions also cause functional and structural changes throughout the brain during the initial phase, and during post-lesional degeneration and regeneration. Bidmon et al. (1997) reported that the distribution pattern and staining intensity of MAP2 in the contralateral cortex appeared normal, although MAP2 immunoreactivity in the perilesional cortex increased.

In the present study, however, 2-7 days after ischemia MAP1A and MAP2 immunoreactivity in
Fig. 4: MAP2 immunoreactivity in the rat cortical coronal section. In the sham cortex, MAP2 immunoreactivity is similarly detected both in contralateral (A) and ipsilateral (B) cortices to infarct region. Two days after insult (C and D), MAP2 immunoreactivity significantly decreased in layers IV and V (arrows indicate layers IV and V). Two months after ischemia, MAP2 immunoreactivity in these regions recovered to the sham level (E and F). Bar = 100 \mu m.
Fig. 5: MAP2 immunoreactivity in the rat hippocampus. In the sham cortex, MAP2 immunoreactivity is similarly detected both in contralateral (A) and ipsilateral (B) hippocampi to infarct region. Two days after insult, MAP2 immunoreactivity in the contralateral hippocampus significantly decreased (C). In the ipsilateral hippocampus, MAP2 immunoreactivity in the hilar region also declined (D). Seven days after ischemia, in the contralateral hippocampus (E), the immunodensity and the distribution of MAP2 immunoreactivity recovered to the sham level, in contrast MAP2 immunoreactivity in the ipsilateral hippocampus (F) was detected in sprouting dendrites of remained hilar neurons and in granule cells (arrows). Bar = 100 μm.
in the ipsi- and contralateral cortices significantly decreased, whereas in layer V, MAP1A immunoreactivity had obviously accumulated in neurons and their processes. This distribution pattern indicates that a time-dependent dramatic growth of neuronal processes, followed by hypoxic ischemia, occurs in the homotopic cortex of the opposite hemisphere. These findings are consistent with those of a previous study, which reported that the widespread degeneration of nerve fibers extending to most of ipsi- and contralateral cortical areas that showed a change of GABAergic inhibition (Witte et al., 2000). Therefore, this result suggests that both MAP1A and MAP2 expressions may be altered in the perilesional cortex, as well as in the contralateral cortex. Furthermore, regarding the elevated Na⁺-K⁺ ATPase immunoreactivity in the contralateral cortex observed in the present study, Jones and colleagues (Jones & Schallert, 1994; Jones et al., 1999) reported that hyperactivity in the contralateral cortex can induce dendritic sprouting or axonal regeneration.

Unexpectedly, 2 days after insult, MAP2 immunoreactivity was significantly decreased within the ipsi- and contralateral hippocampi. This result suggests that remote changes in MAP2 expression following hypoxic ischemia may be evoked within both hippocampi, as was the case in the cerebral cortex. Seven days after ischemia, however, the immunodensity and the distribution of MAP2 immunoreactivity in the contralateral hippocampus recovered to the sham level. In addition, MAP2 immunoreactivity in the ipsilateral hippocampus was detected in sprouting dendrites remaining hilar neurons and in granule cells. With respect to the role of MAP2 in the adult brain, it is viewed that this increased MAP2 immunoreactivity may indicate neuronal plasticity and dendritic sprouting in both hippocampi. The fact is that MAP2 expression is known to increase in the rat brain during remodeling after brain lesions (Johnson & Jope, 1992; Pollard et al., 1994; Stewart et al., 1994; Burnham et al., 1995; Pei et al., 1998). Therefore, the altered MAP2 immunoreactivity may be related to dendritic structural changes of the hilar neurons in response to synaptic activity. In addition, our finding suggests that remote changes after insult may not be restricted to the cerebral cortex but may be associated with various brain regions.

In contrast to MAP2, MAP1A immunoreactivity accumulated in some hilar neurons in both sides of the hippocampus 2 days after insult, and MAP1A immunoreactive axons remained in the contralateral hippocampus 2 months after hypoxic ischemia. In view of the fact that the MAP1 family plays an important role in the maintenance of axonal morphology and axon-like neurite outgrowth (Tucker, 1990), our results suggest that axonal reorganization may be also evoked in both hippocampi, and that this time-dependant alteration may be long lasting compared with the dendritic sprouting.

**CONCLUSIONS**

In conclusion, unilateral (contralateral) elevation of Na⁺-K⁺ ATPase immunoreactivity can prevent cytotoxic edema and reflects the elevated neuronal activity in the contralateral cortex. In addition, this asymmetric hyperexcitability in the cortex may play an important role in the recovery and reorganization of the brain, accompanied by remote changes in MAPs expressions that are not restricted to the cerebral cortex.

**ACKNOWLEDGEMENT**

Na⁺-K⁺ ATPase antibody (a6F) developed by Dr. D. M. Fambrough was obtained from the Developmental Studies Hybridoma Bank developed under the auspices of the NICHD and maintained
REFERENCES

Astrup J. Energy-requiring cell functions in the ischemic brain. Their critical supply and possible inhibition in protective therapy. J Neurosurg 1982; 56: 482-497.

Bidmon HJ, Wu J, Godecke A, Schleicher A, Mayer B, Zilles K. Nitric oxide synthase-expressing neurons are area-specifically distributed within the cerebral cortex of the rat. Neuroscience 1997; 81: 321-330.

Buchkremer-Ratzmann I, Witte OW. Systemically administered cycloheximide reduces inhibition in rat neocortical slice preparation. Brain Res 1996; 743: 329-332.

Burnham WM, Cottrell GA, Diosy D, Racine RJ. Long-term changes in entorhinal-dentate evoked potentials induced by electroconvulsive shock seizures in rats. Brain Res 1995; 698: 180-184.

Forsting M, Reith W, Dorfler A, Meyding-Lamade U, Sartor K. MRI monitoring of experimental cerebral ischaemia: comparison of two models. Neuroradiology 1994; 36: 264-268.

Grafstein B, Forman DS. Intracellular transport in neurons. Physiol Rev 1980; 60: 1167-1283.

Hatashita T, Ito M, Miyao M, Ishii S. Chronological alterations of regional cerebral blood flow, glucose utilization, and edema formation after focal ischemia in hypertensive and normotensive rats. Significance of hypertension. Adv Neurol 1990; 52: 29-37.

Hirokawa N, Funakoshi T, Sato-Harada R, Kanai Y. Selective stabilization of tau in axons and microtubule-associated protein 2C in cell bodies and dendrites contributes to polarized localization of cytoskeletal proteins in mature neurons. J Cell Biol 1996; 132: 667-679.

Huang ZG, Xue D, Preston E, Karbalai H, Buchan AM. Biphasic opening of the blood-brain barrier following transient focal ischemia: effects of hypothermia. Can J Neurol Sci 1999; 26: 298-304.

Johnson GV, Jope RS. The role of microtubule-associated protein 2 (MAP-2) in neuronal growth, plasticity, and degeneration. J Neurosci Res 1992; 33: 505-512.

Jones TA, Chu CJ, Grande LA, Gregory AD. Motor skills training enhances lesion-induced structural plasticity in the motor cortex of adult rats. J Neurosci 1999; 19: 10153-10163.

Jones TA, Schallert T. Use-dependent growth of pyramidal neurons after neocortical damage. J Neurosci 1994; 14: 2140-2152.

Kotila M, Waltimo O. Epilepsy after stroke. Epilepsia 1992; 33: 495-498.

Lagreze HL, Levine RL, Pedula KL, Nickles RJ, Sunderland JS, Rowe BR. Contralateral flow reduction in unilateral stroke: evidence for transhemispheric diastasis. Stroke 1987; 18: 882-886.

Lees GJ. Inhibition of sodium-potassium-ATPase: a potentially ubiquitous mechanism contributing to central nervous system neuropathology. Brain Res Brain Res Rev 1991; 16: 283-300.

Levine S. Anoxic-ischemic encephalopathy in rats. Am J Pathol 1960; 36: 1-14.

Marsden KM, Dell T, Ferralli J, Botteri F, Matus A. Transgenic expression of embryonic MAP2 in adult mouse brain: implications for neuronal polarization. J Neurosci 1996; 16: 3265-3273.

Pei Q, Burnet PJ, Zetterstrom TS. Changes in mRNA abundance of microtubule-associated proteins in the rat brain following electroconvulsive shock. Neuroreport 1998; 9: 391-394.

Pollard H, Khrestchatisky M, Moreau J, Ben-Ari Y, Represa A. Correlation between reactive sprouting and microtubule protein expression in epileptic hippocampus. Neuroscience 1994; 61: 773-787.

Redecker C, Luhmann HJ, Hagemann G, Fritschy JM, Witte OW. Differential downregulation of GABAA receptor subunits in widespread brain regions in the freeze-lesion model of focal cortical malformations. J Neurosci 2000; 20: 5045-5053.

Reinecke S, Lutzenburg M, Hagemann G, Bruehl C, Neumann-Haefelin T, Witte OW. Electrophysiological transcortical diastasis after middle cerebral artery occlusion (MCAO) in rats. Neurosci Lett 1999; 261: 85-88.

Rice JE, Vanucci RC, Brierley JB. The influence of immaturity of hypoxic-ischemic brain damage in the rat. Ann Neurol 1981; 9: 131-141.

Romijn HJ, van Marle J, Janssen AW. Permanent increase of the GAD67/synaptophysin ratio in rat
cerebral cortex nerve endings as a result of hypoxic ischemic encephalopathy sustained in early post-natal life: a confocal laser scanning microscopic study. Brain Res 1993; 630: 315–329.
Romijn HJ, Janszen AW, van Voorst MJ, Buijs RM, Balazs R, Swaab DF. Perinatal hypoxic ischemic encephalopathy affects the proportion of GABA-immunoreactive neurons in the cerebral cortex of the rat. Brain Res 1992; 592: 17–28.
Rosenberg GA. Ischemic brain edema. Prog Cardiovasc Dis 1999; 42: 209–216.
Siesjo BK. Mechanisms of ischemic brain damage. Crit Care Med 1988; 16: 954–963.
So EL, Annegers JF, Hauser WA, O'Brien PC, Whisnant JP. Population-based study of seizure disorders after cerebral infarction. Neurology 1996; 46: 350–355.
Solomon F. Neuroblastoma cells recapitulate their detailed neurite morphologies after reversible microtubule disassembly. Cell 1980; 21: 333–338.
Stewart C, Jeffery K, Reid I. LTP-like synaptic efficacy changes following electroconvulsive stimulation. Neuroreport 1994; 5: 1041–1044.
Stys PK, Waxman SG, Ransom BR. Ionic mechanisms of anoxic injury in mammalian CNS white matter: role of Na+ channels and Na+-Ca2+ exchanger. J Neurosci 1992; 12: 430–439.
Tasker RC, Coyle JT, Vornov JJ The regional vulnerability to hypoglycemia-induced neurotoxicity in organotypic hippocampal culture: protection by early tetrodotoxin or delayed MK-801. J Neurosci 1992; 12: 4298–4308.
Tucker RP. The roles of microtubule-associated proteins in brain morphogenesis: a review. Brain Res Brain Res Rev 1990; 15: 101–120.
Tucker RP, Garner CC, Matus A. In situ localization of microtubule-associated protein mRNA in the developing and adult rat brain. Neuron 1989; 2: 1245–1256.
Witte OW, Bidmon HJ, Schiene K, Redecker C, Hagemann G. Functional differentiation of multiple perilesional zones after focal cerebral ischemia. J Cereb Blood Flow Metab 2000; 20: 1149–1165.