

Neuroprotection in Diabetic Encephalopathy

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Key Words

Diabetes · Encephalopathy · Neuroprotection

Abstract

Increasing evidence has shown that diabetes may be associated with learning and memory deficits in humans. These cognitive disorders, called 'diabetic encephalopathy', can impair the daily performance of diabetic individuals. In recent years, some neuroprotective measures have been proposed to prevent diabetic neuropathology. This review attempts to show a summary of different experimental measures that have been described to improve the burden of diabetes in the central nervous system, particularly hippocampal formation.

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Introductory Remarks

Increasing evidences have shown that diabetes may be associated with learning and memory deficits in humans [1–3]. It seems that diabetes is associated with gradually developing end-organ damage in the central nervous system. This relatively unknown complication can be referred to as 'diabetic encephalopathy' and is characterized by electrophysiological and neuroradiological

changes, such as delayed latencies of evoked potentials, modest cerebral atrophy and (periventricular) white matter lesions [4]. The emerging view is that the diabetic brain features many symptoms that are best described as 'accelerated brain ageing' [5]. Sima et al. [6] suggested two types of diabetic encephalopathy. *Primary diabetic encephalopathy* which is caused by hyperglycemia and impaired insulin action particularly in type 1 diabetes. Apoptotic neuronal loss and cognitive decline is associated with this type in a duration-related fashion. *Secondary diabetic encephalopathy* seems to arise from hypoxic-ischemic insults due to underlying microvascular disease or as a consequence of hypoglycemia [6].

The mechanism(s) by which cognitive abilities are impaired in diabetes has/have not been identified clearly [7]. Recent evidence has shown that the process of neurogenesis, which includes cell proliferation, survival, migration and differentiation, continues in the hippocampal formation well into adulthood in a variety of species, including rodents, nonhuman primates as well as humans [7–11]. Increasing data suggest a diminished neurogenesis as the culprit for diabetic encephalopathy [7, 12, 13]. In conjunction, it is now well understood that the oxidative injury underlies the neuronal injury in the central nervous system following diabetes [14–16].

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Experimental Neuroprotective Measures in Diabetic Encephalopathy

During the last few years, different strategies to prevent and treat diabetic encephalopathy have been considered. Given the underlying mechanisms for diabetic encephalopathy, the neuroprotective measures have focused mainly on the reduction of oxidative stress and the prevention of apoptosis to avoid neuronal loss. In what follows, some of the different experimental measures for neuroprotection in diabetic encephalopathy are described.

Antioxidant Agents

Ates et al. [14] investigated the possible neuroprotective effect of resveratrol against streptozotocin (STZ)-induced hyperglycemia in the rat brain and medulla spinalis. They showed that daily intraperitoneal injection of resveratrol (10 mg/kg) to STZ-induced diabetic rats over 6 weeks can significantly reduce malondialdehyde, xanthine oxidase, and nitric oxide production and increase glutathione levels. Also, Ates et al. [15] demonstrated a significant elevation of malondialdehyde, xanthine oxidase and nitrite levels in the hippocampus, cortex, cerebellum, brain stem and spinal cord of the diabetic rats while a 6-week treatment with etomidate (2 mg/kg/day) provided significantly lower values. Furthermore, they suggested that mexiletine (50 mg/kg/day for 6 weeks) can protect neuronal tissue against diabetic oxidative damage [16].

Kuhad and Chopra [17] investigated the effects of sesamol (3,4-methylenedioxyphenol), a phenolic antioxidant and anti-inflammatory molecule, on cognitive functions, oxidative stress and inflammation in diabetic rats. Their findings showed that chronic treatment with sesamol (2, 4 and 8 mg/kg; p.o.) significantly and dose-dependently attenuated cognitive deficit, and reduced acetylcholinesterase, oxidative stress and inflammation in diabetic rats. They also demonstrated that chronic treatment with curcumin (60 mg/kg; p.o.), a well-established phenolic antioxidant and anti-inflammatory molecule, significantly attenuated cognitive deficit, cholinergic dysfunction, oxidative stress and inflammation in diabetic rats [18]. Tuzcu and Baydas [19] showed that treatment with melatonin and vitamin E significantly ameliorated learning and memory performance. Furthermore, both antioxidants reversed lipid peroxidation and glutathione levels toward their control values.

Muriach et al. [20] treated alloxan-injected diabetic rats with lutein for 10 days. They reported no increase in

malondialdehyde and glutathione concentrations and glutathione peroxidase activity in the retina and hippocampus of lutein-treated rats. Diabetic rats received N-acetylcysteine (1.4–1.5 g/kg body weight) for 8 weeks and demonstrated significantly improved lipid composition, restored membrane fluidity and activity of membrane-bound enzymes. The authors proposed that N-acetylcysteine administration ameliorated oxidative stress and alterations in lipid composition induced by hyperglycemia [21].

Endocrine Hormones

Saravia et al. [22] found that diminished neurogenesis in the dentate gyrus of STZ-induced diabetic adult mice was completely relieved by 10 days after estradiol pellet implantation. In addition, the increased markers of astrogliosis and ongoing neuronal dysfunction were reverted to normal by the estradiol regime that upregulated cell proliferation. They also previously showed that 17 β -estradiol (200 μ g pellet implant in cholesterol during 10 days) can restore dentate gyrus cell proliferation in the diabetic mouse brain [23].

In addition to gene-regulatory effects of insulin and C-peptide on axonal cytoskeletal proteins and nerve fiber integrity, which are favorable in diabetic polyneuropathy, C-peptide is proposed to have some beneficial effects on primary diabetic encephalopathy [24]. It has been shown that C-peptide replacement partially prevents hippocampal neuronal apoptosis and cognitive deficits [25]. Sima et al. [26] showed that full insulinomimetic C-peptide replacement can significantly prevent upregulation of RAGE and NF- κ B in diabetic rat hippocampus. The treatment can be associated with lower expression of TNF- α , IL-1 β , IL-2 and IL-6 in hippocampi of diabetic rats and is likely to improve the oxidative and apoptotic neuronal cell death [26].

Medications

Some heterogenic medications with neuroprotective property have been suggested during recent years. For example, Beauquis et al. [27] examined the neuroprotective efficacy of a selective serotonin reuptake inhibitor, fluoxetine (10 mg/kg/day, i.p., 10 days) in diabetic C57BL/6 mice. They demonstrated that fluoxetine preferentially increased the proliferation of cells with a neuronal phenotype and prevented hilar cell loss within the dentate gyrus [27].

Tsukuda et al. [28] showed that oral administration of nifedipine, a calcium channel blocker, at a nonhypotensive dose (0.001% in laboratory chow) to KK-A(y) type 2

diabetic mice from 10 weeks of age improved cognitive function. Nifedipine treatment decreased the serum insulin level to one fifth of that in KK-A(y) diabetic mice. Moreover, nifedipine treatment significantly reduced superoxide anion production in the brain. Furthermore, treatment with nifedipine markedly reduced the mRNA level of Id-1, an inhibitor of neural differentiation, in the hippocampus. Therefore, Tsukuda et al. [28] concluded that nifedipine ameliorates impaired cognitive function in type 2 diabetic mice, because of attenuation of hyperinsulinemia and superoxide production in the brain and possible upregulation of the neural differentiation-controlling gene, Id-1. Moreover, Tsukuda et al. [29] reported improved cognitive function in KK-A(y) mice by oral administration of candesartan at a nonhypotensive dose (0.005% in laboratory chow). They suggested that candesartan ameliorates the impaired cognitive function in type 2 diabetes mice, because of an increased expression of methyl methanesulfonate sensitive 2, a neuroprotective factor, in addition to improvement of glucose intolerance [29].

Acupuncture

Jang et al. [30] showed that acupuncture at the Zusanli acupoint significantly increased expression of nitric oxide synthase (NOS) under diabetic conditions and proposed that acupuncture treatment may modulate NOS activity in the hippocampus under diabetic conditions. Moreover, it has been documented that acupuncture modulates NOS and neuronal NOS expressions in the cerebral cortex of diabetic rats [31].

Exercise

It has been shown that running on a treadmill (30 min each day) for 8 days is effective in enhancing hippocampal granular cell proliferation in rats with STZ-induced diabetes [32]. In addition, Lee et al. [33] showed a markedly enhanced cell proliferation in the dentate gyrus of hyperglycemic rats which had run on a treadmill for 30 min daily for 10 days. It has also been reported that presynaptic impairment of synaptic plasticity in the dentate gyrus under diabetic conditions may be prevented by treadmill running (17 m/min for 40 min/day, 7 days/week, for 12 weeks) [34].

Radiation

After 0.01 Gy, 0.1 Gy, 1 Gy and 10 Gy radiation was delivered, Kang et al. [35] showed an increase in dentate gyrus proliferating cells and suggested that low doses of radiation (i.e. 0.01 and 0.1 Gy) paradoxically improved

diabetes and induced neuronal cell suppression in the hippocampal dentate gyrus of rats.

Plant Materials

The use of plant materials is increasing in all fields of medicine. Recently, some plant extracts of different geographical origins have been shown to protect the central nervous system against insults of diabetes.

Lim et al. [36] studied the effect of an aqueous extract of *Ginseng radix* on cell proliferation in the dentate gyrus of 7-week-old STZ-induced diabetic rats. They administered the extract at different doses (10, 50, 100, and 200 mg/kg) as well as for different durations (5 and 10 days) under both diabetic and control conditions. *Ginseng radix* had no significant effect on cell proliferation under normal conditions, while it enhanced new cell formation significantly under diabetic conditions. However, the proliferating effect of *Ginseng radix* was observed only at a dose of 50 mg/kg. In addition, there was no significant difference in the number of proliferating cells between 5 and 10 days of treatment. They attributed the observed neuroprotective effects of *Ginseng radix* to saponins which are key pharmacological components of the extract. Previous studies have reported that some groups of saponins increase the release of acetylcholine and the number of choline uptake sites in the rat hippocampus and also increase the expression of choline acetyltransferase in the basal forebrain. The authors concluded that it is possible that ginseng saponin exerts its memory-enhancing effects via upregulating the cholinergic system [36]. Furthermore, Chang et al. [37] showed that administration of *Ginseng radix* suppressed enhanced NOS expression in the hippocampus of diabetic rats and suggested that *Ginseng radix* may aid the treatment of central nervous system complications in diabetes. Jang et al. [38] reported that administration of ginseng radix enhanced the STZ-induced inhibition of c-Fos expression both dose- and duration-dependently and may alleviate this diabetes-induced disturbance in hippocampal functions.

Kim et al. [39] showed that cell proliferation in the dentate gyrus was suppressed in rats with STZ-induced diabetes, and treatment with *Folium mori* was shown to increase new cell formation in the dentate gyrus in both normal rats and those with STZ-induced diabetes. In addition, treatment with *F. mori* in normal rats and those with STZ-induced diabetes was shown to enhance neuropeptide Y expression in the dentate gyrus. It has been concluded that the increase in the expression of neuropeptide Y in the dentate gyrus induced by the treatment

with *F. mori* may be associated with the observed effect of *F. mori* extract on cell proliferation. The authors suggested that *F. mori* treatment may aid in the recovery from the central nervous system complications of diabetes mellitus by enhancing cell proliferation in the dentate gyrus via augmented neuropeptide Y expression.

Shin et al. [40] reported that treatment with 50–200 µg/kg/day of the aqueous extract of *Rhizoma anemarrhenae* for 7 days increased new cell formation and neuropeptide Y expression in the dentate gyrus of diabetic rats which was reduced by treatment with STZ in rats.

Fazeli et al. [41] showed that the administration of the hydroalcoholic extract of nettle (*Urtica dioica*, 100 mg/kg/day) for 4 weeks stopped diabetes-induced granule cell loss within the dentate gyrus of STZ-induced diabetic rats. They suggested that the nettle extract can ameliorate cognitive dysfunction seen in diabetes. Gülçin et al. [42] described some antioxidant properties of nettle extract including inhibition of fatty acid peroxidation, effective reduction of power, free radical scavenging, superoxide anion radical scavenging, hydrogen peroxide scavenging, and metal chelating activities. In addition, the level of free electron accumulation in several rat brain areas such as the right frontal lobe has been decreased following nettle leaf supplementation [43, 44]. In conjunction with antioxidant activity, it was documented that the nettle extract may have anti-apoptotic and cell survival-supporting effects [44].

Aucubin is an iridoid glycoside that is commonly found in plants. Xue et al. [45] proposed that administration of aucubin (5 mg/kg; i.p.) in diabetic rats can improve unfavorable changes in pyramidal cell ultrastructure, proportions of apoptotic cells and survivability of neuronal cells by modulating the expressions of Bcl-2 and Bax genes. In addition, it has been documented that aucubin at doses of 0, 1, 5 or 10 mg/kg can show some neuroprotective properties probably through promotion of endogenous antioxidant enzymatic activities [46].

New Prospective for Future Researches

Some new strategies, agents and interventions are under study in other fields which may have some potential neuroprotective property in diabetic encephalopathy. For example, exogenous erythropoietin showed some potential for neuroprotection in brain ischemia or trauma. It has been found that exogenous erythropoietin infusion can improve the ischemic damage of hippocampal CA1 neurons and ischemia-induced learning deficits. Furthermore, enhanced cognitive functioning in a conditioned taste aversion mouse model has been reported fol-

lowing intraperitoneal exogenous erythropoietin administration [47]. Now, it is demonstrated that reductions of brain temperature may be associated with robust neuroprotection for hypoxia-ischemia in the brain of laboratory animals. In addition, Laptook [48] proposed some therapeutic benefits of hypothermia for term infants with hypoxic-ischemic encephalopathy. It is supposed that hypothermia may modify multiple cascades of events that contribute to brain injury. The finding may be beneficial for cognitive deficits seen in diabetic individuals. Inflammatory cascades and mediators including transcription factors are considered to contribute to the postischemic neuroinflammation. The binding agonists of PPAR isoforms (a transcription factor) showed some neuroprotection in ischemic brain probably through preventing inflammatory gene expression, inducing antioxidant enzymes and other neuroprotective transcripts. Consequently, PPAR-γ agonists and similar agents can be developed as future therapeutics for ischemic as well as diabetic encephalopathy [49].

Ischemic preconditioning has been associated with some neuroprotective benefits. It was shown that ischemic preconditioning can inhibit the cytosolic release of cytochrome C and reduce the activation of caspase-9 activation. These mitochondrial changes following ischemic preconditioning can mediate the potential neuron-preserving property against apoptosis [50].

Concluding Remarks

Neuroprotection in diabetic encephalopathy is a newly opened up venue in medical research. The reversibility of hippocampal neuropathology through the modulation of the neurogenesis within the dentate gyrus might give hope for different potential measures which can up-regulate cell proliferation and compensate the neuronal loss. Furthermore, a variety of new antioxidants/anti-apoptotic agents and interventions as neuroprotective agents can be found against the underlying oxidative injury as well as neuronal apoptosis.

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References

- 1 Biessels GJ, Kappelle AC, Bravenboer B, Erkelens DW, Gispen WH: Cerebral function in diabetes mellitus. *Diabetologia* 1994; 37:643–650.
- 2 Liang XC, Guo SS, Hagino N: Current status of clinical and experimental researches on cognitive impairment in diabetes. *Chin J Integr Med* 2006;12:68–74.
- 3 Brands AM, Biessels GJ, de Haan EH, Kappelle LJ, Kessels RP: The effects of type 1 diabetes on cognitive performance: a meta-analysis. *Diabetes Care* 2005;28:726–735.
- 4 Brands AMA, Kessels RPC, de Haan EHF, Kappelle LJ, Biessels GJ: Cerebral dysfunction in type 1 diabetes: effects of insulin, vascular risk factors and blood glucose levels. *Eur J Pharmacol* 2004;490:159–168.
- 5 Biessels GJ, van der Heide LP, Kamal A, Bleys RLAW, Gispen WH: Ageing and diabetes: implications for brain function. *Eur J Pharmacol* 2002;441:1–14.
- 6 Sima AAF, Kamiya H, Li ZG: Insulin, C-peptide, hyperglycemia, and central nervous system complications in diabetes. *Eur J Pharmacol* 2004;490:187–197.
- 7 Jackson-Guilford J, Leander JD, Nisenbaum LK: The effect of streptozotocin-induced diabetes on cell proliferation in the rat dentate gyrus. *Neurosci Lett* 2000;293:91–94.
- 8 Gould E, Tanapat P, Rydel T, Hastings N: Regulation of hippocampal neurogenesis in adulthood. *Biol Psychiatry* 2000;48:715–720.
- 9 Gould E, Gross CG: Neurogenesis in adult mammals: some progress and problems. *J Neurosci* 2002;22:619–623.
- 10 Cameron HA, Gould E: Adult neurogenesis is regulated by adrenal steroids in the dentate gyrus. *Neuroscience* 1994;61:203–209.
- 11 Gould E, Tanapat P: Lesion-induced proliferation of neuronal progenitors in the dentate gyrus of the adult rat. *Neuroscience* 1997;80:427–436.
- 12 Zhang WJ, Tan YF, Yue JT, Vranic M, Wojtowicz JM: Impairment of hippocampal neurogenesis in streptozotocin-treated diabetic rats. *Acta Neurol Scand* 2008;117:205–210.
- 13 Beauquis J, Saravia F, Coulaud J, Roig P, Dardenne M, Homo-Delarche F, De Nicola A: Prominently decreased hippocampal neurogenesis in a spontaneous model of type 1 diabetes, the nonobese diabetic mouse. *Exp Neurol* 2008;210:359–367.
- 14 Ates O, Cayli SR, Yucel N, Altinoz E, Kocak A, Durak MA, Turkoz Y, Yologlu S: Central nervous system protection by resveratrol in streptozotocin-induced diabetic rats. *J Clin Neurosci* 2007;14:256–260.
- 15 Ates O, Yucel N, Cayli SR, Altinoz E, Yologlu S, Kocak A, Cakir CO, Turkoz Y: Neuroprotective effect of etomidate in the central nervous system of streptozotocin-induced diabetic rats. *Neurochem Res* 2006;31:777–783.
- 16 Ates O, Cayli SR, Altinoz E, Yucel N, Kocak A, Tarim O, Durak A, Turkoz Y, Yologlu S: Neuroprotective effect of mexiletine in the central nervous system of diabetic rats. *Mol Cell Biochem* 2006;286:125–131.
- 17 Kuhad A, Chopra K: Effect of sesamol on diabetes-associated cognitive decline in rats. *Exp Brain Res* 2008;185:411–420.
- 18 Kuhad A, Chopra K: Curcumin attenuates diabetic encephalopathy in rats: behavioral and biochemical evidences. *Eur J Pharmacol* 2007;576:34–42.
- 19 Tuzcu M, Baydas G: Effect of melatonin and vitamin E on diabetes-induced learning and memory impairment in rats. *Eur J Pharmacol* 2006;537:106–110.
- 20 Muriach M, Bosch-Morell F, Alexander G, Blomhoff R, Barcia J, Arnal E, Almansa I, Romero FJ, Miranda M: Lutein effect on retina and hippocampus of diabetic mice. *Free Radic Biol Med* 2006;41:979–984.
- 21 Kamboj SS, Chopra K, Sandhir R: Hyperglycemia-induced alterations in synaptosomal membrane fluidity and activity of membrane bound enzymes: beneficial effect of N-acetylcysteine supplementation. *Neuroscience* 2009;162:349–358.
- 22 Saravia FE, Beauquis J, Revsin Y, Homo-Delarche F, de Kloet ER, De Nicola AF: Hippocampal neuropathology of diabetes mellitus is relieved by estrogen treatment. *Cell Mol Neurobiol* 2006;26:943–957.
- 23 Saravia F, Revsin Y, Lux-Lantos V, Beauquis J, Homo-Delarche F, De Nicola AF: Oestradiol restores cell proliferation in dentate gyrus and subventricular zone of streptozotocin-diabetic mice. *J Neuroendocrinol* 2004; 16:704–710.
- 24 Sima AA, Zhang W, Li ZG, Kamiya H: The effects of C-peptide on type 1 diabetic polyneuropathies and encephalopathy in the BB/Wor-rat. *Exp Diabetes Res* 2008;2008: 230458.
- 25 Sima AA, Kamiya H: Is C-peptide replacement the missing link for successful treatment of neurological complications in type 1 diabetes? *Curr Drug Targets* 2008;9:37–46.
- 26 Sima AA, Zhang W, Kreipke CW, Rafols JA, Hoffman WH: Inflammation in diabetic encephalopathy is prevented by C-peptide. *Rev Diabet Stud* 2009;6:37–42.
- 27 Beauquis J, Roig P, Homo-Delarche F, De Nicola A, Saravia F: Reduced hippocampal neurogenesis and number of hilar neurones in streptozotocin-induced diabetic mice: reversion by antidepressant treatment. *Eur J Neurosci* 2006;23:1539–1546.
- 28 Tsukuda K, Mogi M, Li JM, Iwanami J, Min LJ, Sakata A, Fujita T, Iwai M, Horiuchi M: Diabetes-associated cognitive impairment is improved by a calcium channel blocker, nifedipine. *Hypertension* 2008;51:528–533.
- 29 Tsukuda K, Mogi M, Li JM, Iwanami J, Min LJ, Sakata A, Fujita T, Iwai M, Horiuchi M: Amelioration of cognitive impairment in the type-2 diabetic mouse by the angiotensin II type-1 receptor blocker candesartan. *Hypertension* 2007;50:1099–1105.
- 30 Jang MH, Shin MC, Lim BV, Kim HB, Kim YP, Kim EH, Kim H, Shin MS, Kim SS, Kim CJ: Acupuncture increases nitric oxide synthase expression in hippocampus of streptozotocin-induced diabetic rats. *Am J Chin Med* 2003;31:305–313.
- 31 Jang MH, Shin MC, Kim YP, Kim EH, Kim CJ: Effect of acupuncture on nitric oxide synthase expression in cerebral cortex of streptozotocin-induced diabetic rats. *Acupunct Electrother Res* 2003;28:1–10.
- 32 Kim HB, Jang MH, Shin MC, Lim BV, Kim YP, Kim KJ, Kim EH, Kim CJ: Treadmill exercise increases cell proliferation in dentate gyrus of rats with streptozotocin-induced diabetes. *J Diabetes Complications* 2003;17: 29–33.
- 33 Lee HH, Shin MS, Kim YS, Yang HY, Chang HK, Lee TH, Kim CJ, Cho S, Hong SP: Early treadmill exercise decreases intrastriatal hemorrhage-induced neuronal cell death and increases cell proliferation in the dentate gyrus of streptozotocin-induced hyperglycemic rats. *J Diabetes Complications* 2005; 19:339–346.
- 34 Reisi P, Babri S, Alaei H, Sharifi MR, Mohaddes G, Lashgari R: Effects of treadmill running on short-term pre-synaptic plasticity at dentate gyrus of streptozotocin-induced diabetic rats. *Brain Res* 2008;1211:30–36.
- 35 Kang JO, Kim SK, Hong SE, Lee TH, Kim CJ: Low dose radiation overcomes diabetes-induced suppression of hippocampal neuronal cell proliferation in rats. *J Korean Med Sci* 2006;21:500–505.
- 36 Lim BV, Shin MC, Jang MH, Lee TH, Kim YP, Kim HB, Lee KS, Kim H, Kim EH, Kim CJ: Ginseng radix increases cell proliferation in dentate gyrus of rats with streptozotocin-induced diabetes. *Biol Pharm Bull* 2002;25: 1550–1554.
- 37 Chang HK, Jang MH, Lim BV, Lee TH, Shin MC, Shin MS, Kim H, Kim YP, Kim EH, Kim CJ: Administration of Ginseng radix decreases nitric oxide synthase expression in the hippocampus of streptozotocin-induced diabetic rats. *Am J Chin Med* 2004;32:497–507.
- 38 Jang MH, Chang HK, Shin MC, Lee TH, Kim YP, Kim EH, Kim CJ: Effect of ginseng radix on c-Fos expression in the hippocampus of streptozotocin-induced diabetic rats. *J Pharmacol Sci* 2003;91:149–152.
- 39 Kim H, Jang MH, Shin MC, Chang HK, Lee TH, Lim BV, Jung CY, Lee CY, Kim EH, Kim CJ: *Folium mori* increases cell proliferation and neuropeptide Y expression in dentate gyrus of streptozotocin-induced diabetic rats. *Biol Pharm Bull* 2003;26:434–437.

- 40 Shin MS, Kim SK, Kim YS, Kim SE, Ko IG, Kim YS, Kim CJ, Kim YM, Kim BK, Kim TS: Aqueous extract of *Anemarrhena* rhizome increases cell proliferation and neuropeptide Y expression in the hippocampal dentate gyrus on streptozotocin-induced diabetic rats. *Fitoterapia* 2008;79:323–327.
- 41 Fazeli SA, Gharravi AM, Ghafari S, Jahanshahi M, Gholipour MJ: The granule cell density of the dentate gyrus following administration of *Urtica dioica* extract to young diabetic rats. *Folia Morphol* 2008;67:196–204.
- 42 Gülçin I, Küfrevioğlu ÖI, Oktay M, Büyükkuroğlu ME: Antioxidant, antimicrobial, antiulcer and analgesic activities of nettle (*Urtica dioica* L.) *J Ethnopharmacol* 2004;90:205–215.
- 43 Pieroni A, Janiak V, Durr CM, Ludeke S, Trachsel E, Heinrich M: In vitro antioxidant activity of non-cultivated vegetables of ethnic Albanians in southern Italy. *Phytother Res* 2002;16:467–473.
- 44 Toldy A, Stadler K, Sasvári M, Jakus J, Jung KJ, Chung HY, Berkes I, Nyakas C, Radák Z: The effect of exercise and nettle supplementation on oxidative stress markers in the rat brain. *Brain Res Bull* 2005;65:487–493.
- 45 Xue H, Jin L, Jin L, Zhang P, Li D, Xia Y, Lu Y, Xu Y: Neuroprotection of aucubin in primary diabetic encephalopathy. *Sci China C Life Sci* 2008;51:495–502.
- 46 Xue HY, Jin L, Jin LJ, Li XY, Zhang P, Ma YS, Lu YN, Xia YQ, Xu YP: Aucubin prevents loss of hippocampal neurons and regulates antioxidative activity in diabetic encephalopathy rats. *Phytother Res* 2009;23:980–986.
- 47 Noguchi CT, Asavaritikrai P, Teng R, Jia Y: Role of erythropoietin in the brain. *Crit Rev Oncol Hematol* 2007;64:159–171.
- 48 Laptook AR: Use of therapeutic hypothermia for term infants with hypoxic-ischemic encephalopathy. *Pediatr Clin North Am* 2009;56:601–616.
- 49 Yi JH, Park SW, Kapadia R, Vemuganti R: Role of transcription factors in mediating post-ischemic cerebral inflammation and brain damage. *Neurochem Int* 2007;50:1014–1027.
- 50 Chen L, Liu K, Xie D, Sercombe R, Liu Y: Inhibition of caspase-9 activation and apoptosis is involved in ischemic preconditioning-induced neuroprotection in rat brain. *Neurol Res* 2007;29:855–861.