Themed Section: Midkine

REVIEW

Midkine in repair of the injured nervous system

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Midkine (MK) is a growth factor with neurotrophic and neurite outgrowth activities. It was expressed in the peri-ischaemic area in the acute phase of cerebral infarction in rat brains. Astrocytes were the origin of MK in this occasion. MK has been assessed in terms of its effects on neural injury. The administration of MK into the lateral ventricle immediately prior to ischaemia prevented cell death in the hippocampal CA1 neurons degenerated by transient forebrain ischaemia in gerbils. MK administration was also beneficial in rats with neural injury, especially after kainic acid-induced seizures. Gene therapy with mouse MK cDNA using an adenovirus was effective in reducing the cerebral infarction volume and in increasing the number of neuronal precursor cells in the subventricular zone of the rat brain. MK mRNA and MK protein were found in spinal cord motor neurons of the anterior horn in both the acute phase of sciatic nerve injury and 3 weeks later. MK immunoreactivity was also found in the proximal side of a sciatic nerve-injured site in sciatic nerve axons. MK receptors were expressed in Schwann cells after injury, suggesting crosstalk between axons and Schwann cells. MK was also present in nerve terminals and influenced ACh receptor clustering during neuromuscular development in *Xenopus*. Thus, MK may also be involved in reinforcing and maintaining the synapse. All these findings indicate the therapeutic potential of MK for promoting repair of the nervous system after injury.

LINKED ARTICLES

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Abbreviations

AP-1, activator protein-1; bFGF, basic fibroblast growth factor; EAE, experimental autoimmune encephalitis; ENU, ethylnitrosourea; GCI, glial cytoplasmic inclusion; GFAP, glial fibrillary acidic protein; LRP, low-density lipoprotein receptor-related protein; MCA, middle cerebral artery; MK, midkine; NE, neuroepithelial; NGF, nerve growth factor

Introduction

Midkine (MK) was discovered in the differentiation system of embryonal carcinoma cells as the product of a gene respond-ing to a morphogen, retinoic acid (Kadomatsu *et al*., 1988). MK is now known to be widely distributed throughout ver-tebrates and to exhibit various activities in addition to the originally described heparin-binding capacity (Muramatsu, 2014). Notably, MK promoted neurite extension, survival and migration of embryonic neurons (Muramatsu and Muramatsu, 1991; Michikawa *et al*., 1993; Muramatsu *et al*., 1993; Maeda *et al*., 1999).

MK is strongly expressed in embryonic tissues including those in the nervous system (Kadomatsu *et al*., 1990) and its expression was observed as early as the starting period of neurogenesis in both frogs and mice (Sekiguchi *et al*., 1995; Fan *et al*., 2000), and injection of MK mRNA into early *Xenopus* embryos promoted neurogenesis (Yokota *et al*., 1998). MK was also detected in neural precursor cells and was found to enhance their growth and survival (Zou *et al*., 2006). MK was also shown to be strongly expressed in migrating neurons and radial glial processes in the midgestational period (Matsumoto *et al*., 1994), in which neurons migrate from the ventricular zone to the pial surface. In contrast to

robust expression of MK in embryonic period (Kadomatsu et al., 1990), MK expression in the adult is restricted (Muramatsu, 2014). In mice, MK was reported to be strongly expressed only in the kidney after birth (Kadomatsu et al., 1990).

In this review, we will deal with the role of MK in repair of the injured nervous system, focusing to ischaemic brain injury and sciatic nerve injury. Some related subjects such as muscular injury will be briefly mentioned. General information on MK is available elsewhere (Muramatsu, 2010; 2014; Kadomatsu et al., 2013)and there is an earlier review dealing with MK and diseases of the CNS (Muramatsu, 2011).

MK in brain injury

Soon after the discovery of MK, this growth factor was found to have neurotrophic activity and association with neural diseases. Thus, neurons isolated from the fetal spinal cords and sympathetic ganglions gradually became necrotic in culture, and MK inhibited this neuronal death (Michikawa et al., 1993). Furthermore, the senile plaque characteristic of Alzheimer's disease was positive for anti-MK immunoreactivity (Yasuhara et al., 1993). Therefore, we examined whether MK, which is a neurotrophic factor, but is essentially considered to be an embryonic protein, was expressed in adults at neuronal injury sites as well as in the fetus.

Experimental cerebral infarction was induced under craniotomy and subsequent left middle cerebral artery (MCA) occlusion with a bipolar electric coagulator in rats (Yoshida et al., 1995). MK was found to be strongly expressed in the peri-ischaemic area 1 day after the insult. A peak in MK expression was seen after 2 days, whereas MK immunoreactivity was not found after 10 days. As above, the expression of MK was shown in the acute phase, in which marked inflammation was observed in the ischaemic area, and tissue repair started from the subacute phase to the chronic stage. Because MK expression has been considered to occur very early, clarification of its role became an important subject.

The expression of glial fibrillary acidic protein (GFAP) was shown in astrocytes 2–3 days after that of MK. GFAP expression subsequently continued for a long period of time, and activator protein-1 (AP-1) responsive element were known to exist in the promoter regions of MK (Uehara et al., 1992) and GFAP genes. The expression of AP-1, consisting of the products of oncogene C-Jun and C-Fos, also started very early, 6–12 h after cell damage. Basic fibroblast growth factor (bFGF) and nerve growth factor (NGF) were also expressed in the peri-ischaemic area in the acute phase of cerebral infarction. Because MK, as well as bFGF and NGF, exhibits neurotrophic activity, we considered that MK might be involved in neural repair.

Astrocytes were thought to be responsible for the production of MK as MK was found in isolated astrocytic culture supernatants from fetal brains, but not in neuronal or oligodendroglial culture supernatants (Satoh et al., 1993) and astrocytes surrounding the cerebral infarction area were shown to be positive for anti-MK and anti-GFAP with double immunostaining (Wang et al., 1998). From its amino acid sequence with a signal peptide, MK has been considered to be a secretory protein. However, MK-immunoreactivity was predominantly found in cytoplasm. Later, Shibata et al. (2002) showed that MK can be secreted and taken up by the secreting cells to act in an autocrine manner. Thus, a proportion of MK may have been secreted and re-uptaken into astrocytes even upon cerebral infarction.

In agreement with the proposal that astrocytes are the origin of MK, MK protein and MK mRNA were also found in astrocytes following forebrain ischaemia, which caused neuronal death in the hippocampal CA1 region of rats after the occlusion of four blood vessels (bilateral common carotid and vertebral arteries) for 20 min following the method of Pulsinelli (Mochizuki et al., 1998). Furthermore, the astrocytes were positively stained for imunnoreactive MK in injury sites in the acute phase of spinal cord compression injury, using a weight placed on the thoracic spinal cord of rats (Sakakima et al., 2004b).

On the basis of the data discussed above, the general conclusion is that MK is secreted from astrocytes. However, it is not always the case. Among neurodegenerative diseases, in the brain samples of patients with multiple system atrophy, glial cytoplasmic inclusions (GCIs), which are disease specific, were shown to be present in oligodendrocytes. These GCIs were contained immunoreactive MK (Kato et al., 2000) and it was suggested that MK was generated in response to oligodendroglial degeneration caused by GCI. Such results show that the expression of MK is not confined to astrocytes.

Expression of MK at the early stage of cerebral infarction prompted us to examine its role in repair processes. At that time, MK was shown to protect retinal photoreceptor cells from damaging effects of exposure to constant light (Unoki et al., 1994) but there were no reports of the in vivo effects of MK on neuronal cells in the central or peripheral nervous systems. Whether neuronal death could be inhibited by the administration of MK was examined in a forebrain ischaemia model using gerbils (Yoshida et al., 2001). Forebrain ischaemia caused hippocampal CA1 neuronal death in gerbils 4 days after the ischaemic insult, which can be achieved by performing bilateral common carotid artery occlusion for 5 min because of the imperfect ring of Willis and underdeveloped collateral circulation in this animal. Hippocampal CA1 neuronal death was inhibited, when 0.5, 1 and 2 μg of MK were given into the lateral ventricle just before ischaemia but MK was not effective when given 2 h after ischaemia. Although the therapeutic time window of the MK treatment was very narrow, this is a result suggesting the feasibility of neurotrophic factor therapy (Yoshida et al., 2001).

It has been argued that obtaining an ameliorative effect in transient forebrain ischaemia in gerbils is relatively easy. Delayed neuronal death was shown to occur through a biochemical process in the gerbil forebrain ischaemia model (Weinachter et al., 1990). Large quantities of the neurotransmitter glutamate are released in ischaemic areas, which in turn increased intracellular calcium levels. Thus, in the gerbil model, the ameliorative effect of drugs is easy to obtain using antagonists to calcium ion flux or NMDA (Weinachter et al., 1990). However, in our unpublished data, MK was shown to have no influence on intracellular calcium concentrations in neuronal cell cultures.

Furthermore, MK was effective even in cerebral infarction in rats (Y. Yoshida et al., unpublished experiments). The cerebral infarction volume was reduced by 45% when 10 μg of

MK was injected into the cerebral ventricle, in the rat cerebral infarction model using the Koizumi procedure, in which a nylon suture as the embolus was inserted from the right internal carotid to the MCA, and recanalization of MCA was performed 60 min after occlusion (Harvey *et al.*, 2004). Administration of MK into rat brain was also effective in ameliorating kainic acid-induced seizures, which is a model of temporal lobe epilepsy (Kim *et al.*, 2010). In this experiment, 0.4 μg of MK was provided simultaneously with kainic acid. Although kainic acid caused extensive degeneration of hippocampal neurons, MK largely rescued the affected neurons.

Gene therapy employing MK also shows promise. A replication-deficient recombinant adenovirus-encoding mouse MK was injected into the lateral ventricle 1.5 h after cerebral infarction, with a photothrombotic MCA occlusion model in spontaneous hypertensive rats with the photosensitive pigment Rose Bengal (i.v. administration). The cerebral infarction volume was found to be decreased by 40% with the treatment (Takada *et al.*, 2005). We estimated that the MK doses administered in this model were over 150 μg as the MK protein. The number of neuronal precursor cells that migrated in the subventricular zone after 7 days was higher in the treated group than in the untreated group (Ishikawa *et al.*, 2009).

Analysis of injured fetal brain suggests that MK is also involved in normal brain development and its repair during fetal period. Intense expression of MK was detected in radial glial processes and neurons when neurons migrated from the ventricular zone to the pial surface in the midgestational period (Matsumoto *et al.*, 1994). The developing brains of mice prenatally exposed to ^{60}Co γ-irradiation were examined at the most radiosensitive stage with immunohistochemistry using an anti-MK antibody (Sun *et al.*, 1997). MK existed only on the cell surface, consistent with the view that it is one of the membrane-bound extracellular matrix proteins (Matsumoto *et al.*, 1994). The anti-MK antibody was utilized for staining of radial glial fibres. Irradiation caused scattered and incomplete radial glial fibres on embryonic days 13–17 in the telencephalic wall, and post-natal mouse brains exhibited abnormal histologies (Sun *et al.*, 1997; 1999). The findings indicated that MK might be involved in the promotion of neuronal migration and associated with brain developmental events such as neural differentiation and neural network formation in the fetal brain (Sun *et al.*, 1997).

When the DNA synthesis inhibitor ethylnitrosourea (ENU) was given to mother rats on embryonic day 16, the effect persisted until 48 h later and, fetal brain neuroepithelial (NE) cells, migrating neuroblasts and radial glial fibres were damaged 16–24 h after administration. The apoptotic cells and the cells in the M-phase of mitosis in the ventricular zone were MK positive. After administration of ENU, there was arrest of NE cells in the G-1 phase at 4–8 h, cell cycle synchronization of most NE cells to the S-phase at 16 h and to the M-phase at 24 h, and recovery of many NE cells by 48 h. MK expression was not essential for every cell cycle phase of NE cells but it was necessary to maintain the M-phase of NE cells (Kikuchi-Horie *et al.*, 2004). Therefore, MK was also considered to be involved in repair of fetal brain injury.

The clinical relevance of these animal studies is not clear as expression of MK in patients is difficult to study. We encountered no fatalities in patients in the acute phase because even patients with serious cerebral infarction typically survived for at least 1 week. Only 1 of 10 autopsied brain samples from patients with acute cerebral infarction was shown to express MK (Y. Yoshida *et al.*, unpublished data).

As MK has beneficial effects on repair of neural damage, it is relevant to investigate how its levels could be increased. MK was strongly expressed in the cerebral peri-infarct area, following an exercise intervention following cerebral infarction in a rat (Matsuda *et al.*, 2011). Other neurotrophic factors such as glia-derived neurotrophic factor, NGF and FGF were also expressed after the exercise intervention (Neeper *et al.*, 1996; Gomez-Pinilla *et al.*, 1998; Kim *et al.*, 2005). Whether the expression of MK is increased by exacerbating ischaemia with exercise, only occurs due to loss of energy with degeneration or is connected to the recovery, repair and plasticity of the brain is still being investigated. Exercise intervention also caused a decrease in the infarction volume, and we presume that the last possibility mentioned might be the correct one. Finally, it should be noted that MK was expressed in injured brain cells of adults and further studies might even detect large amounts of MK in certain places of adult bodies.

Sciatic nerve injury and MK

The sciatic nerve injury model is frequently used to investigate regeneration of injured peripheral nerve. We have examined the expression of MK after sciatic nerve injury in rats. The right sciatic nerve was injured using a microspatula chilled with liquid nitrogen, leading to Waller degeneration and soleus muscle atrophy. The sciatic nerve regenerated and arrived at the soleus again after 3–4 weeks of slow outgrowth, with muscle atrophy rapidly recovering thereafter. MK was shown to be expressed in ventral horn motor neurons on the ipsilateral injury side in the acute phase, and also in sciatic nerve axons (Sakakima *et al.*, 2004a). This expression was biphasic, as it disappeared 2 weeks later, and MK was expressed again after 3 weeks. Low levels of MK were expressed in the contralateral anterior horn neuron, together with ipsilateral expression (Sakakima *et al.*, 2004a). Schwann cells in the distal side of the injury stopped myelination, leading to demyelination.

We also examined expression of MK receptors, which comprise several molecules (Muramatsu, 2014). Immunoreactivities of the two important receptor molecules, namely those of low-density lipoprotein receptor-related protein (LRP) and receptor-type protein tyrosine phosphataseζ were found in Schwann cells and myelin. However, MK immunoreactivity was also found in axons (Sakakima *et al.*, 2004a). Because crosstalk has been observed among axons and Schwann cells, MK may be used for communication between axons and Schwann cells.

Schwann cells grow excessively in malignant neurilemmoma and benign neurofibromatosis type I due to a deficiency in tumour suppressor gene *NF1* (Mashour *et al.*, 2001). MK, rather than bFGF, PDGF or pleiotrophin was thought to be strongly involved in the growth of these tumours. It is clear that MK enhanced Schwann cell proliferation in these

tumours; however, MK may promote Schwann cell differentiation during peripheral nerve regeneration, as mentioned earlier.

MK mRNA was found in the CNS, but not in peripheral nerves. However, MK protein was identified in the peripheral neuromuscular junction during development in *Xenopus*. MK influenced ACh receptor clustering and was involved in the formation of synapses (Zhou *et al.*, 1997). Pleiotrophin is reversely secreted from the postsynaptic membrane to the nerve terminals and strengthens the connection of the synapse, whereas MK appears to maintain synapse transmission in an orthodromic direction (Zhou *et al.*, 1997). Thus, even in the nerve injury, MK can be produced by the spinal cord and transported through the peripheral nerves.

The role of MK in regeneration of peripheral nerves and its effects on the innervated muscle was studied using genetically altered mice. When sciatic nerve degeneration and regeneration, following cold injury, were examined in MK gene-deficient mice (Mdk–/–) (Nakamura *et al.*, 1998), recovery was delayed compared with wild-type mice (Mdk+/+) (Sakakima *et al.*, 2009). In Mdk+/+ mice, marked demyelination and axonal degeneration were found in an axial transverse section, focused to the distal portion of the lesion in the sciatic nerve in the acute phase, and regenerated nerve fibres were found after 3–4 weeks. However, in Mdk–/– mice, the amount of demyelination observed was very slight, with most of the axon still being myelinated after 1 week. Regenerated fibres appeared after 4 weeks; however, the number of fibres was less in Mdk–/– mice than in Mdk+/+ mice. As above, degeneration was markedly slower in Mdk–/– mice, but regeneration was also delayed in these mice.

Regeneration in Mdk–/– mice 3 weeks after injury appeared to be 1 week behind that of Mdk+/+ mice. The weight of the soleus muscle decreased, whereas its weight in Mdk–/– mice was heavier than that in Mdk+/+ mice 1 week after injury. However, the weight of the soleus muscle 3 weeks after injury in Mdk–/– mice was less than that in Mdk+/+ mice. The weight of the soleus muscle in Mdk–/– mice became the same as that in Mdk+/+ mouse 5 weeks after injury. As above, degeneration slowly progressed in Mdk–/– mice, as regeneration did, and a delay in regeneration of approximately 1 week was observed in Mdk–/– mice.

To evaluate functional aspects of the regeneration, electromyograms were recorded after electrical stimulation of the proximal part of the lesion in the sciatic nerve. In Mdk+/+ mice, the evoked potentials emerged in the soleus 2 weeks after injury, and the amplitude of these potentials was high 4 weeks after injury. However, in Mdk–/– mice, soleus electromyograms were first observed much later, 5 weeks after injury. Although the regeneration of the sciatic nerve was only slightly delayed. We consider that many neurotrophic factors are involved in peripheral nerve regeneration, and the effect of deficiency of a single factor is a modest one. These findings agree with the slight delay in regeneration even in cerebral infarction and spinal cord injury models in Mdk–/– mice (Y. Yoshida *et al.*, in preparation).

As above, MK is involved in both degeneration and regeneration of peripheral nerves after injury, and as a whole is beneficial for regeneration (Figure 1). Consistent with this conclusion, a similar result was obtained concerning liver regeneration. In the process of liver regeneration, the migra-
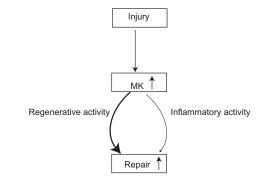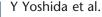

Figure 1

Midkine (MK) is induced by injury and can either support repair or potentiate injury, depending on the level of the inflammation accompanying the initiating injury. When there is a relatively low level of inflammation, as in the CNS, peripheral nerves, heart, liver or muscle, MK promotes repair. When there is marked inflammation, as in the kidney, blood vessels, post-surgical adhesions, antibody-induced arthritis or EAE, the effects of MK are harmful as they reinforce the inflammatory changes and delay repair.

tion of neutrophils and macrophages to the liver 1–5 days after partial hepatectomy was suppressed in Mdk–/– mice. Liver damage was also less severe as assessed by serum aspartate aminotransferase levels in Mdk–/– mice. However, cell growth in the liver was generally suppressed in Mdk–/– mice and liver weights 7 and 14 days after hepatectomy were significantly less in Mdk–/– mice than in Mdk+/+ mice (Ochiai *et al.*, 2004).

MK in related diseases

The role of MK in repair of injured muscle is similar to that found in repair of peripheral nerve. MK expression was observed in myoblasts, myotube cells in the process of regeneration following skeletal muscle injury, but was not found before injury. Muscle injury was induced by injecting bupivacaine hydrochloride into rat tibialis anterior muscles. These muscles were restored, regenerated and differentiated from muscle satellite cells to myofibres in approximately 15 days. MK expression was widely observed, successively, from myoblasts to myotube cells. It was strongly expressed in myotube cells 5–7 days after injury, whereas MK expression was not found in mature myofibres or resting satellite cells (Sakakima *et al.*, 2006). The regenerating muscle cells were immunopositive for one of the MK receptors, LRP. Thus, a possible function of MK is influencing the differentiation of skeletal muscle (Sakakima *et al.*, 2006).

The role of MK induced by muscle injury was also examined using MK-deficient mice. Muscle regeneration after the injection of bupivacaine hydrochloride into tibialis anterior muscles was delayed in Mdk–/– mice, and the diameter of myotubes was significantly smaller in Mdk–/– mice than in Mdk+/+ mice 5 and 7 days after injury. No significant difference was observed between these mice at 14 days (Ikutomo *et al.*, 2013). However, the number of macrophages in the injured muscle, as assessed by the expression of a macrophage

marker, was significantly lower in Mdk–/– mice than in Mdk+/+ mice 3 days after injury. These results indicate that the deletion of MK results in a delay in regeneration of injured muscle preceded by the decreased migration of macrophages to the damaged area (Ikutomo et al., 2013).

Pathological effects of MK were evident in experimental autoimmune encephalitis (EAE), induced by the administration of myelin oligodendrocyte glycoprotein. MK expression was significantly up-regulated after induction of EAE (Liu et al., 1998) but the symptoms of EAE were very mild in Mdk–/– mice, compared with those in Mdk+/+ mice (Wang et al., 2008). Regarding pathophysiology, MK was shown to inhibit the phosphorylation of STAT5 by increasing the activity of the tyrosine phosphatase SHP-2, which in turn reduced Foxp3 expression. The number of CD4+CD25+regulatory T-cells was decreased in the presence of MK, such that autoimmune reactions were reinforced by self-responsive Th1/Th17 cells. In Mdk–/– mice, inflammation was ameliorated by increasing the infiltration of CD4+CD25+regulatory T-cells to the site of inflammation. EAE in wild-type mice could be markedly inhibited with an i.p. administered anti-MK RNA aptamer once daily in 15 mg·kg⁻¹ as a maximal dose for 2 days (Wang et al., 2008). An RNA aptamer consists of nucleic acids, inhibits function of the target molecule and sometimes is called RNA antibody.

Increased inflammation caused by MK is not restricted to EAE but observed in many inflammatory diseases such as ischaemic renal failure (Sato et al., 2001), neointima formation after ischaemic injury (Horiba et al., 2000) and antibody-induced arthritis (Maruyama et al., 2004). However, MK did not activate astrocytes and microglia (Muramoto et al., 2013) but is considered to significantly contribute to neuro-inflammation. When inflammation is at a mild level, decreased inflammation in Mdk–/– mice is often correlated with decreased or delayed regeneration, as observed in repair of peripheral nerve (Sakakima et al., 2009). Whether MK promotes the repair or accelerates tissue injury induced by inflammation, depends on the organ and tissues involved (Muramatsu, 2010; Kadomatsu et al., 2013). Inflammation in CNS is well known to injure the highly elaborate neural circuits.

MK is expressed in various kinds of brain tumours. Because growth factors are closely associated with oncogenesis, they are expected to be involved in the growth of brain tumour cells. MK was shown to be immunopositive in 19 of 32 glioblastoma samples, in 2 of 14 astrocytoma samples and in 0 of 10 oligodendrocytoma samples (Kato et al., 1999). MK staining was also found in the cytoplasm. The positive rate was slightly higher in metastatic brain tumours,with 4 of 6 samples being positive in brain metastases from breast cancer. A correlation was found between positive staining of the cell proliferation marker non-histone nuclear protein and MK. A correlation between MK expression and tumour progression was also found in astrocytomas (Mishima et al., 1997). Furthermore, MK expression in glioblastomas is also important from a therapeutic viewpoint. A conditionally replicating adenovirus, which was constructed using a promoter region of MK, eradicated xenografted glioblastoma but showed no effects on normal brain cells (Kohno et al., 2004).

MK levels in CSF can be determined by an ELISA. The levels were unexpectedly high in humans without neurological

disease (0.37 ± 0.21 ng·mL⁻¹, $n = 46$, mean $\pm$ SD) (Yoshida et al., 2008). We investigated the origin of MK in CSF. For that purpose, rat brains were removed and fixed after the perfusion with physiological saline containing heparin. MK immunoreactivity in these brains was found in epithelial cells of the cerebral ventricle choroid plexus. We consider that these cells produce and secrete MK, which is taken up by these cells in an autocrine manner. MK levels were not significantly elevated in the CSF of patients with cerebrovascular disorders but were elevated in patients with meningitis (Yoshida et al., 2008). MK may be secreted by infiltrating leukocytes at meningitis lesions because MK is a cytokine acting upon inflammation, and was expressed weakly in mononuclear cells in an autopsy sample from a patient (Yoshida et al., 2008). However, although MK is an inflammatory cytokine, is also a neurotrophic factor and is thought to have a protective effect on brain cells, comparable to those already discussed for MK and injury of peripheral nerves and muscles.

Conclusion

MK expression was found in the acute phase just after cerebral infarction or sciatic nerve injury. The mechanism by which MK is expressed in the acute phase is a subject of current investigation. Repair begins from the acute phase, and MK appears to be involved in inflammation, angiogenesis, construction of the subsequent nerve network, and the formation and maintenance of the synapse. Therefore, the application of exogenous MK or the up-regulation of endogenous MK expression, should be beneficial in the treatment of various injuries in the nervous system.

Acknowledgements

Conflict of interest

None declared.

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