BJP British Journal of Pharmacology

DOI:10.1111/bph.12571
www.brjpharmacol.org

Themed Section: Midkine

EDITORIAL

Midkine: an emerging target of drug development for treatment of multiple diseases

Takashi Muramatsu[1]* and Kenji Kadomatsu[2]

[1]*Department of Health Science, Faculty of Psychological and Physical Science, Aichi Gakuin University, 12 Araike, Iwasaki-cho, Nisshin, Aichi 470-0195, Japan, and* [2]*Department of Biochemistry, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan*

Correspondence
Takashi Muramatsu or Kenji Kadomatsu
E-mail:
tmurama@med.nagoya-u.ac.jp or
kkadoma@nagoya-u.ac.jp

*Present status and address: Professor Emeritus, Nagoya University, 1204 Hirabariminami 2, Tenpaku, Nagoya 468-0020, Japan.

Keywords
bone remodeling; cancer, cardiovascular diseases; inflammatory diseases; immune system; midkine; neural diseases; neurogenesis; oocyte maturation; renal diseases

Midkine is a multifunctional factor and has anti-apoptotic, migration-promoting, angiogenic, anti-microbial and other activities. Midkine ameliorates ischemic injury in the heart and brain, enhances oocyte maturation, and is involved in neurogenesis. On the other hand, midkine is an important factor in the etiology of various diseases, especially those with inflammatory backgrounds. Furthermore, midkine is overexpressed in most malignant tumors and plays roles in their invasive phenotypes as well as in their resistance to chemotherapeutics. Therefore, midkine itself is expected to be useful for the treatment of brain and heart diseases, while midkine inhibitors are promising for the treatment of malignant tumors, multiple sclerosis, restenosis, renal diseases, hypertension and osteoporosis. Blood levels of midkine are also expected to be helpful as disease markers, especially as cancer markers.

LINKED ARTICLES
This article is part of a themed section on Midkine. To view the other articles in this section visit http://dx.doi.org/10.1111/bph.2014.171.issue-4

Molecular cloning and human genome sequencing has revealed a number of medically important proteins and genes. This information is being utilized to develop new pharmaceuticals to treat life-threatening diseases such as cancer. In this respect, a protein, midkine, is attracting broad interest and is the subject of the present special issue.

Midkine is a growth factor or cytokine and enhances the survival, migration and many other activities of target cells. Midkine is rich in both basic amino acids and cysteine, and is not related to most other growth factors/cytokines. It is the founding member of a protein family, the other member of which is pleiotrophin. It is strongly expressed during embryonic periods, especially at the midgestation stage, and plays important roles in development, especially in neurogenesis. On the other hand, midkine expression in adult tissue is generally weak or undetectable. However, it is induced upon injury and exerts many activities related to tissue repair, for example, enhancement of the survival of injured cells and recruitment of inflammatory leukocytes. Indeed, induced midkine ameliorates ischemic injury of the heart and brain. However, as the result of increased inflammation, midkine has been implicated in the etiology of various diseases, namely renal diseases, restenosis, rheumatoid arthritis, adhesion after surgery and multiple sclerosis. Studies using midkine-deficient mice and administration of midkine or its inhibitors established the involvement of midkine not only in the above-mentioned diseases in experimental models but also in wider range of diseases, such as hypertension and osteoporosis. Furthermore, midkine is expressed in most malignant tumors and is a key factor associated with its invasive phenotypes. Thus, both midkine and pharmaceuticals targeting midkine are considered to be helpful for the treatment of various diseases.

This special issue starts with an introductory review on the structure and function of midkine (Muramatsu, 2014). In addition to a general description of the protein and genomic

© 2014 The British Pharmacological Society

structure of midkine, detailed information is given about the functional roles of each segment of midkine. Notably, midkine with an extended N-terminal sequence has different properties, raising the possibility that manipulation of the N-terminal sequence might yield midkine with an extended half life. The evolutionary origin of midkine is also discussed. Midkine is conserved in vertebrates, and a related molecule is present in *Drosophila melanogaster*. After summarizing the physiological activity of midkine, and its role in pathological processes, up-to-date knowledge is provided on midkine receptors and the downstream signaling system. Several proteins have been indicated to be midkine receptors, such as receptor protein tyrosine phosphatase ζ, low-density lipoprotein receptor-related proteins, Notch2, integrins, anaplastic lymphoma kinase and neuroglycan C. In certain cases, these receptors appear to form a complex to increase specificity and affinity.

With regard to molecular evolution, midkine shows an interesting duplication in zebrafish (Winkler and Yao, 2014). Two midkine paralogues, *mdka* and *mdkb*, found in zebrafish show distinct expression profiles during development, but both are preferentially expressed in the nervous system. Dynamic changes of midkine expression are also observed during development of mammalian nervous system. In addition, many reports demonstrate that midkine plays diverse roles in the nervous system, e.g., neuroprotection and neurodifferentiation. Winkler and Yao address the roles of midkine in nervous system formation and maintenance by summarizing latest findings in the field (Winkler and Yao, 2014).

Gramage *et al*. focus on the expression and function of midkine in the retina (Gramage *et al*, 2014). *mdka* is expressed in the retinal progenitors in zebrafish, while *mdkb* is expressed in newly post-mitotic cells. Light-induced death of photoreceptors in adults induces up-regulation of both two midkine paralogues in proliferating Muller glia, which serves as the intrinsic stem cell in regenerative neurogenesis, and photoreceptor progenitors. It is also interesting that *mdka* expression shows a circadian rhythm in the adult zebrafish retina.

Since midkine promotes the survival of injured neuronal cells, it has attracted attention from the viewpoint of therapy for various neuronal diseases. Pioneering research has been performed on ischemic brain injury (Yoshida *et al*., 2014). Midkine is expressed around the infarcted area at the early stage of cerebral infarction. Administration of midkine or adenovirus vector with midkine cDNA can ameliorate cerebral ischemic injury.

As shown by the comprehensive review by Herradón and Pérez-García (2014), midkine and pleiotrophin exert neuroprotective effects against drug-abuse-induced neurotoxicity and neurodegenerative disorders. Exogenous administration of midkine or pleiotrophin by non-invasive methods, such as nasal administration, into the central nervous system is proposed to become a novel therapeutic strategy for addictive and neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease.

Midkine enhances *in vitro* maturation of oocytes, and consequently post-fertilization development (Ikeda and Yamada, 2014). This midkine activity is considered to be mediated by anti-apoptotic effects on cumulus-granulosa cells surrounding oocytes, and is of interest from veterinary as well as medical aspects. Since this discovery, other neurotrophic factors have also been shown to have oocytetrophic activities. Among the many neurotrophic factors, midkine and pleiotrophin play physiologically important roles in oocyte maturation, since mice doubly deficient in both midkine and pleiotrophin are mostly infertile.

Bone remodeling requires an organized regulation of bone-formation and bone- resorption. Therefore, coordinated activities of osteoblasts and osteoclasts are essential. These cellular activities are regulated by various factors, including growth factors, such as RANKL (receptor activator of NF-κB), BMP (bone morphogenic protein), WNT and TGFβ (transforming growth factor-β). Midkine is expressed during bone formation and fracture repair. By demonstrating a striking difference between wild-type and midkine-deficient mice, Liedert *et al*. propose that midkine is a negative regulator of bone formation and mechanically induced bone remodeling (Liedert *et al*., 2014).

Midkine shares several properties with antibacterial proteins of the innate immune system (Gela *et al*., 2014). Indeed, midkine appears to be a component of the system; it was found to have potent bactericidal and fungicidal activities, and is constitutively expressed at barriers of the body, such as in the skin (Gela *et al*., 2014). Midkine is an interesting molecule, serving as a template to develop novel pharmaceutical strategies to counteract infections, especially to those by pathogens resistant to antibiotics.

A typical example of midkine involvement in inflammatory diseases is experimental autoimmune encephalomyelitis, the model of multiple sclerosis (Takeuchi, 2014). Midkine augments the symptoms of the disease by decreasing populations of regulatory T cells and tolerogenic dendritic cells, which elicit differentiation of the former cells. Importantly, an RNA aptamer targeting midkine ameliorates the disease without apparent side effects, raising the possibility of clinical application of the reagent.

Both acute kidney injury and chronic kidney disease are life-threating diseases. Midkine is involved in acute and chronic inflammation of the kidney (Sato and Sato, 2014). Midkine-deficient mice show much less renal damage, as compared with wild-type, in ischemia reperfusion injury, an acute kidney injury model. Chronic kidney disease is often accompanied by hypertension and diabetic nephropathy. Midkine-deficient mice also show less renal damage in these disease models. It is particularly interesting that midkine is involved in hypertension associated with chronic kidney disease. Thus, 5/6 nephrectomy, a chronic kidney disease model, induces hypertension in wild-type mice, but not midkine-deficient mice. Midkine is up-regulated in the lung, where it activates the renin-angiotensin pathway and consequently increases blood pressure. Therefore, in this disease, midkine functions as a factor which mediates kidney-lung interaction.

Inflammatory cell recruitment by midkine causes a variety of pathological changes. Atherosclerosis is a representative status of inflammation of the blood vessel wall in which midkine is also involved (Kadomatsu *et al*., 2014). On the other hand, midkine exerts an anti-apoptotic activity, which leads to acute cardioprotection after cardiac infarction. Acute cardioprotection by midkine and its angiogenic activity also protect the heart from cardiac remodeling, which

causes chronic heart failure. However, the angiogenic activity may also promote cancer. Therefore, midkine is a double-edged sword, but an intriguing drug target for different cardiovascular diseases. Further investigations, including verification of the mechanisms of midkine action, its chronic toxicity and optimal therapeutic dosing regimen, will open an avenue of its clinical application.

As another role of midkine in immune function, it enhances the survival of mature B cells (Cohen and Shachar, 2014). There are three key elements in maintenance of peripheral B-cell homeostasis, namely 1) B cell receptor tonic signals, 2) the B cell activating factor, and 3) CD74, its ligand (macrophage migration inhibitory factor) and downstream molecules. Midkine and hepatocyte growth factor are components of the 3rd element (Cohen and Shachar, 2014). Midkine also plays a role in the survival of malignant B cells. Therefore, suppression of midkine-dependent survival pathway might be considered for treatment of B cell malignancies.

Midkine is generally overexpressed in diverse malignant tumors, and enhances the survival, migration and angiogenic activity of tumor cells. Strong expression of midkine is correlated with a worse prognosis of patients with a tumor and its chemotherapy resistance. Thus, midkine has been considered to be a promising target for therapy of many kinds of malignant tumors.

Kishida and Kadomatsu describe a basic strategy targeting midkine for cancer therapy (Kishida and Kadomatsu, 2014). Midkine trapping by antibodies, an RNA aptamer or a fragment of midkine receptor has been reported to be effective in suppression of tumor growth. RNAi technologies inhibiting midkine expression are also successful to suppress cancer. Neuroblastoma, a pediatric cancer, is a candidate cancer for a therapy targeting midkine. Blood level of midkine is closely correlated with patient prognosis (higher midkine level shows worse prognosis). RNA aptamer trapping of midkine significantly suppresses growth of neuroblastoma cells *in vitro* as well as *in vivo*. Since Notch2 signaling is markedly affected by midkine trapping, the axis of midkine and Notch2 may be involved in tumor development of neuroblastoma.

Another example, in which midkine-targeting therapy is promising, is pancreatic cancer, more specifically pancreatic ductal adenocarcinoma, one of the deadliest cancers. Midkine is overexpressed in about 50% of pancreatic cancer, and confers chemotherapy resistance on tumor cells through the Notch2 signaling pathway (Güngör *et al.*, 2014).

Blood and urinary midkine levels are elevated in malignant diseases and in certain other diseases such as renal diseases. Thus, midkine is also promising as a disease marker.

In addition to the potential application of midkine and its antagonists mentioned above, midkine might be also helpful to culture stem cells, and midkine promoter is useful for cancer-specific expression of toxic genes and cytolytic viruses (Erguven *et al.*, 2012). Practical information on the development of midkine and its inhibitors as therapeutics has been also reviewed (Muramatsu, 2011).

Finally, because of its involvement in various diseases, efforts to develop therapies based on midkine and its inhibitors will be rewarding, especially because successful therapy for a specific disease will be applicable to a wide variety of diseases after modification.

Acknowledgements

We are grateful to Dr. Péter Ferdinandy for valuable suggestions to this special issue.

References

Cohen S, Shachar I (2014). Midkine as a regulator of B cell survival in health and disease. Br J Pharmacol 171: 888–895.

Erguven M, Muramatsu T, Bilir A (Eds) (2012). Midkine: from embryogenesis to pathogenesis and therapy. Dordrecht: Springer.

Gela A, Jovic S, Nordin SL, Egesten A (2014). Midkine in host defense. Br J Pharmacol 171: 859–869.

Gramage E, Li J, Hitchcock P (2014). The expression and function of midkine in the vertebrate retina. Br J Pharmacol 171: 913–923.

Güngör C, Hofmann BT, Wolters-Eisfeld G, Bockhorn M (2014). Pancreatic Cancer. Br J Pharmacol 171: 849–858.

Herradón G, Pérez-García C (2014). Targeting midkine and pleiotrophin signaling pathways in addiction and neurodegenerative disorders: recent progress and perspectives. Br J Pharmacol 171: 837–848.

Ikeda S, Yamada M (2014). Midkine and cytoplasmic maturation of mammalian oocytes in the context of ovarian follicle physiology. Br J Pharmacol 171: 827–836.

Kadomatsu K, Bencsik P, Görbe A, Csonka C, Sakamoto K, Kishida S, Ferdinandy P (2014). Therapeutic potential of midkine in cardiovascular diseases. Br J Pharmacol 171: 936–944.

Kishida S, Kadomatsu K (2014). Involvement of midkine in neuroblastoma tumorigenesis. Br J Pharmacol 171: 896–904.

Liedert A, Schinke T, Ignatius A, Amling M (2014). The role of midkine in skeletal remodeling. Br J Pharmacol 171: 870–878.

Muramatsu T (2011). Midkine: a promising molecule for drug development to treat diseases of the central nervous system. Curr Pharm Des 17: 410–423.

Muramatsu T (2014). Structure and function of midkine as the basis of its pharmacological effects. Br J Pharmacol 171: 814–826.

Sato W, Sato Y (2014). Midkine in nephrogenesis, hypertension and kidney diseases. Br J Pharmacol 171: 879–887.

Takeuchi H (2014). Midkine and multiple sclerosis. Br J Pharmacol 171: 931–935.

Winkler C, Yao S (2014). The midkine family of growth factors: diverse roles in nervous system formation and maintenance. Br J Pharmacol 171: 905–912.

Yoshida Y, Sakakima H, Matsuda F, Masako I (2014). Midkine in repair of the injured nervous system. Br J Pharmacol 171: 924–930.