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Review

A Review of Signal Transduction of Endothelin-1 and Mitogen-activated Protein Kinase-related Pain for Nanophysiotherapy

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Abstract. [Purpose] An understanding of pain is very important in the study of nanophysiotherapy. In this review, we summarize the mechanisms of endothelin-1 (ET-1)- and mitogen-activated protein kinase (MAPK)-related pain, and suggest their applications in pain physiotherapy. [Method] This review focuses on the signal transduction of pain and its mechanisms. [Results] Our reviews show that mechanisms of ET-1- and MAPK-related pain exist. [Conclusions] In this review article, we carefully discuss the signal transduction in ET-1- and MAPK-related pain with reference to pain nanophysiotherapy from the perspective of nanoparticle-associated signal transduction.
Key words: Endothelin-1, Pain, Signal transduction

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INTRODUCTION

Endothelin-1 (ET-1) belongs to a family of 21-amino acid residue peptides is expressed, in different patterns, in various tissues and cells[1, 2)] (Fig. 1A). ET-1 plays a role in controlling muscle contraction, cell proliferation, and cell activity[1, 2)]. It has been reported that the protein kinase C (PKC) pathway, mitogen-activated protein kinases (MAPKs) pathway, and myosin light chain kinase (MLCK)-activated pathway contribute to ET-1-induced contraction[1, 2)]. In particular, DOCA-dependent hypertension is recognized as an important component of MAPK-related ET-1[1)]. ET-1 can be released in response to chemical or physical stimuli, such as in response to the vasoactive amine norepinephrine, hypoxic stimulation, and ischemia[2, 3)]. In normal physiology conditions, ET-1 is expressed at a low level in plasma[4, 5)]. It was reported that the level of plasma ET-1 is increased in hypertension and myocardial infarction and that it can be used as a biomarker of cardiovascular disorders[4, 5)]. Furthermore, ET-1 plays a role in cell growth, apoptosis, muscle contraction, and inflammation through MAPK activations[1, 2)]. These MAPKs include extracellular signal-regulated protein kinase-1 and kinase-2 and the p38 mitogen-activated protein. Studies have confirmed that these are related to ET-1 in eukaryotic cells[1, 2)]. Meanwhile, studies have also reported that the MAPK pathway plays an important part in the mechanism of hyperalgesia and allodynia[6, 7)]. ET-1 is produced and secreted from the dorsal root ganglion, spinal cord, and peripheral nerves[8)]. ET-1 acts as a pain inhibitor in the central nervous system, whereas it can cause painful sensitivity, as hyperalgesia and allodynia, in the peripheral nerve system[9–11)]. However, the mechanism underlying ET-1- and MAPK-related pain is still unknown. The purpose of this review was to elucidate the ET-1- and MAPK-related pain mechanism and to contribute to future studies of pain nanophysiotherapy from the perspective of nanoparticle-associated signal transduction (Fig. 1B).

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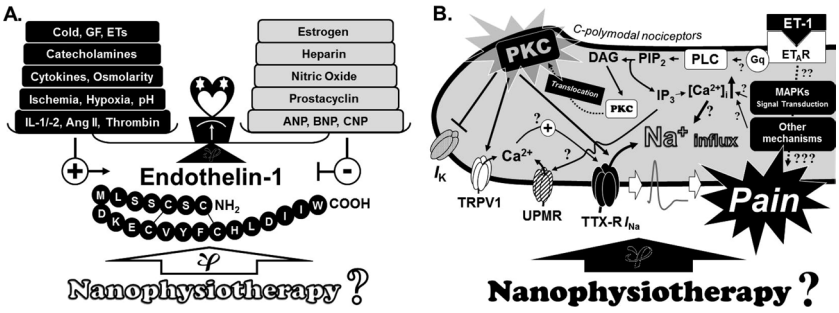

Fig. 1. Schematic representation of mechanisms of endothelin-1-related pain in nanophysiotherapy.

ETs, endothelins; IL-1/-2; interleukin-1 and -2; AngII, angiotensin II; GF, growth factor; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; NH_2, amino group; COOH, carboxyl group; C, cysteine; S, serine; L, leucine; M, methionine; D, aspartic acid; K, lysine; E, glutamic acid; V, valine; Y, tyrosine; F, phenylalanine; H, histidine; I, isoleucine; W, tryptophan; ET-1, endothelin-1; ET_AR, subtype A of endothelin receptor; PKC, protein kinase C; Gq, subtype q of trimeric GTP-binding protein; PIP_2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; DAG, diacylglycerol; IP_3, inositol 1,4,5-triphosphate; $[Ca^{2+}]_i$, intracellular or cytosolic Ca^{2+}; Ik, delayed rectifier K^+ currents; TRPV1, transient receptor potential cation channel subfamily V member 1 also known as the the vanilloid receptor 1; UPMR, unique plasma membrane-bound receptor; TTX-R I_{Na}, tetrodotoxin-resistant voltage-gated Na^+ currents; MAPKs, mitogen-activated protein kinases.

1. Mechanisms of endothelin-1-related pain for nanophysiotherapy

ET-1 is present in the brain, spinal cord, sympathetic ganglia, and spinal ganglion in mammals, including humans, and it is thought to play a significant part in the pain signaling system[8, 10, 12, 13]. ET-1 produces different reactions in the central and peripheral nervous systems[10, 11, 13]. Injection of ET-1 into the periaqueductal gray area and the spinal cord results in an antinociceptive effect, whereas injection into the peripheral nervous system results in hyperalgesia and pain reactions[10, 11, 13, 14]. ET-1 is also produced in numerous cells, including inflammatory and cancer cells. According to some reports, excessive levels of ET-1 are released following skin damage[15, 16]. ET-1 increases sensitivity to harmful chemical stimuli such as capsaicin[17, 18]. Meanwhile, PKC induces the creation of action potential in neuron of pain transmission[19–22]. ET-1 appears to be involved in the activation of PKC[23, 24] (Fig. 1B). The ET-1 receptor is activated during activation of the ET-1-induced polymodal-C nociceptor[25]. The catalytic response of the trimeric guanosine triphosphate-binding protein by receptor activation can activate phospholipase C[2, 26] (Fig. 1B). Although phospholipase C shows tissue specificity, it promotes an influx of extracellular Ca^{2+} from a unique plasma membrane-bound receptor and voltage-gated Ca^{2+} channel through the creation and activation of inositol 1,4,5-triphosphate[2, 27, 28] (Fig. 1B). The increased intracellular Ca^{2+} in response to the ET-1 stimulus transmits pain signals to the primary sensory area, leading to amplification of tetrodotoxin-resistant voltage-gated Na^+ currents[10, 16, 29] (Fig. 1B). Diacylglycerol induced by the activation of ET-1 also activates PKC[18, 29]. The activation mechanism is comprised of a translocation process that inactivates PKC present in the cytoplasm transfer to cell membrane[2, 18, 30]. However, more study is necessary to elucidate the pain mechanism of ET-1 using the transcutaneous electrical nerve stimulation or interferential current treatment from the perspective of nanoparticle-associated signal transduction (Fig. 1B).

2. Mitogen-activated protein kinases and pain mechanisms for nanophysiotherapy

There are two types of pain mechanisms that induce inflammation and hyperalgesia. The first is the signal transmission pathway through adenylate cyclase (also called adenylyl cyclase, which is a 12-transmembrane protein)-linked protein kinase A, and the second is the transmission pathway through phospholipase C-related PKC[31–33]. Furthermore, previous studies have reported that hyperalgesia is involved in the MAPK signal pathway in addition to the protein kinase A and PKC pathway[7, 34–36]. Hyperalgesia can be induced by three sources: an injection of substance P into the dura mater, an instillation injection of capsaicin in the large intestine, and the release of cytokines, such as interleukin-1β[7, 34]. However, the exact mechanism underlying allodynia is not known. It has been suggested that a severed A-β fiber terminal regenerated by lamina of Rexed II or trans-synaptic degeneration in the spinal dorsal horn may contribute to the development of allodynia[37, 38]. Allodynia induced by sympathetic nerve excitement has been attributed to noradrenergic sprouting around the dorsal root ganglion or nerve fibers in damaged peripheral nerves[39, 40]. Other studies have reported that the peripheral nerve termi-

nal and an increase in the spontaneous discharge in dorsal root ganglion cells create allodynia[41, 42]. In particular, studies have emphasized the importance of MAPK because the MAPK pathway is involved in allodynia in the same way as spinal nerve ligation[6, 43]. More study is needed on MAPK-related pain control using physical factors for pain control from the perspective of nanophysiotherapy[44–47] (Fig. 1B).

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