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Role of EPAC1 in chronic pain

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ABSTRACT

Chronic pain usually lasts over three months and commonly occurs in chronic diseases (cancer, arthritis, and diabetes), injuries (herniated discs, torn ligaments), and many major pain disorders (neuropathic pain, fibromyalgia, chronic headaches). Unfortunately, there is currently a lack of effective treatments to help people with chronic pain to achieve complete relief. Therefore,it is particularly important to understand the mechanism of chronic pain and find new therapeutic targets. The exchange protein directly activated by cyclic adenosine monophosphate(cAMP) (EPAC) has been recognized for its functions in nerve regeneration, stimulating insulin release, controlling vascular pressure, and controlling other metabolic activities. In recent years, many studies have found that the subtype of EPAC, EPAC1 is involved in the regulation of neuroinflammation and plays a crucial role in the regulation of pain, which is expected to become a new therapeutic target for chronic pain. This article reviews the major contributions of EPAC1 in chronic pain.

1. Introduction

Pain is defined as unpleasant feelings and emotional experiences caused by tissue damage or potential tissue damage. It can be classified as physiological (acute) or pathological (chronic) pain [1]. Chronic pain usually lasts over three months and is seen in chronic diseases (cancer, arthritis, and diabetes), injuries (herniated discs, torn ligaments), and many major pain disorders (neuropathic pain, fibromyalgia, chronic headaches) [2]. Chronic pain seriously affects the quality of life of patients, not only brining physical pain to patients but also increasing the financial burden on patients' families [3]. Unfortunately, as the mechanisms of chronic pain are complex and varied, there is currently a lack of effective treatments to help people with chronic pain achieve complete relief. Therefore, it is particularly significant to understand the mechanism of chronic pain and find new therapeutic targets.

EPAC directly activated by cAMP is a guanine nucleotide exchange factor of Ras-like (rat sarcoma, Ras) small GTPase, which can function independently of protein kinase A (PKA), a downstream effector of the second messenger cAMP [4]. EPAC1 has been recognized for its functions in nerve regeneration, stimulating insulin release, controlling vascular pressure, and controlling other metabolic activities [5–7]. Upregulation of EPAC1 expression is commonly associated with hypersensitivity of nociceptive neurons and hyperalgesia [8] which has been validated in many pain models such as the complete Freund's adjuvant (CFA)model, the chronic constriction model and diabetic neuropathy [9–12]. EPAC has been studied in many chronic pain conditions. Activation of EPAC1 in postsurgical pain may induce local postoperative recovery processes and may be an important mechanism for controlling chronic postoperative pain [13]. Modulation of persistent postoperative pain in rats via the EPAC1/PKC-betaII (protein kinase C, PKC) pathway has been shown in a postoperative tonic pain model [14]. Furthermore, EPAC1 may act synergistically with other anesthetic drugs such as propofol to co-regulate the spinal GluN2B-p38MAPK pathway to alleviate postoperative pain in animal models of postoperative pain [15]. In chronic inflammatory pain caused by disease, EPAC1 and the associated cAMP pathway also play a key role. Tim B et al. have demonstrated that EPAC act as pivotal regulators in the onset and/or maintenance of pain caused by inflammation and injury in rats [16]. Chronic pain caused by diabetes was significantly alleviated by reducing the expression of EPAC1 and following activated G protein coupled receptor kinase 2 (GRK2) which has been studied in rats [17]. Berkey and colleagues found that in rats, EPAC1 and downstream regulators play a role in pain relief in bone cancer pain [18]. Since then, the role of EPAC1 in pain has been gradually discovered thus implies the significance of

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the regulation of EPAC1 for the prevention and treatment of chronic pain [19].

In this review, we focus on the regulatory mechanisms of EPAC1 in chronic pain, highlighting their potential as a therapeutic target and diagnostic tool.

2. Structural characteristics and function of EPAC1 in the nervous system

2.1. Structure of EPAC

EPAC includes two subunits, EPAC1 and EPAC2, encoded by RAPGEF3 and RAPGEF4, respectively. EPAC, a multi-domain protein, contains an N-terminal regulatory region and a C-terminal catalytic region. The regulatory region is responsible for the subcellular localization of EPAC and contains a cyclic nucleotide binding (CNB) domain and the dishevelled–EGL–pleckstrin homology (DEP) domain for localization. EPAC2A has an additional CNB domain at the N-terminal while EPAC2C is lack of DEP domain. The catalytic region is composed of the Ras exchange motif (REM), Ras-associated (RA) domain, and CDC25 homology domain (CDC25HD) [20] (Fig. 1a). Unbound EPAC (apo) is inactive, CNB covers the CDC25HD domain, and when cAMP binds, CDC25HD is exposed, and cytoplasmic EPAC is rapidly translocated to the plasma membrane, activating Ras-like small GTPase, causing a series of biological effects [21–23](Fig. 1b).

2.2. Function of EPAC1 in the nervous system

The expression of EPAC in the central nervous system of rats has been found to be regulated by development. EPAC1 is significantly expressed in the embryo and newborn period, and significantly decreased in the adult period, while EPAC2 is actively expressed in the adult period in rats [24]. EPAC is involved in many processes both inside and outside the nervous system, including the stabilization of the blood-brain barrier, axon guidance and regeneration, learning and memory, and neuroinflammation [25–29]. EPAC1 contributes to the protection of the blood-brain barrier. Nikolaos Kakogiannos et al. showed that activation of EPAC helps to strengthen endothelial barrier function. The immunoglobulin superfamily protein JAM-A promotes the activation and ligand localization of the small GTPase Rap-1 (Ras-related protein-1) through sustained expression of EPAC-1 and EPAC2 which in turn enhance endothelial barrier function, and can ameliorate blood-brain barrier breakdown after ischemia-reperfusion injury by EPAC-Rap-1 and other pathways in mice [28,30,31]. EPAC also plays an important role in neuroprotection and regeneration. The activation of EPAC is similar to that of cAMP agonists in mediating cAMP-dependent axon growth and regeneration in rat dorsal root ganglion (DRG) neurons [32]. EPAC knockdown can inhibit the growth-promoting effect of cAMP on axon regeneration [32,33]. However, the relative contribution of EPAC and PKA to axon guidance remains to be explored. EPAC is a negative regulator of myelination and is expected to be a therapeutic target for myelin-related diseases [27,34]. EPAC also takes part in mood regulation and may play a key role in combating pathological states such as anxiety and depression [35,36]. Moreover, EPAC1 has the potential to relieve neuroinflammation that commonly contributes to pain hypersensitivity [37]. Monoamine oxidase B inhibitors reduce the expression of lipopolysaccharide(LPS)-induced proinflammatory factors by acting on the cAMP-PKA/EPAC signaling cascade, indicating the potential of EPAC to combat inflammation in a cervical epithelial cell line [38]. Inhibition of EPAC1 in hippocampal neurons can reduce mitochondrial superoxide levels, and block iron oxidation, thereby preventing peroxide damage to the brain [39], and relieving hippocampal neuroinflammation. Studies of EPAC-related pathways provide a therapeutic direction for the treatment of neuroinflammation-related pain.

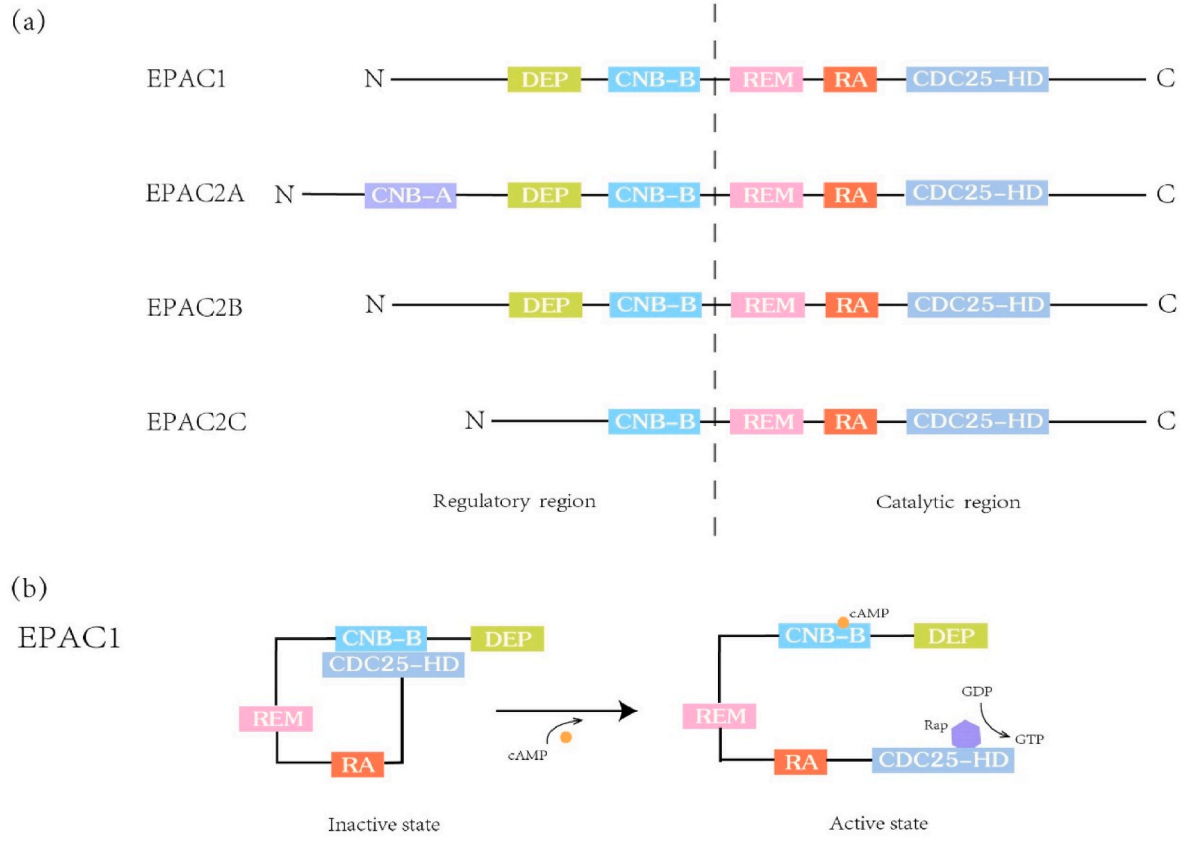

Fig. 1. Structure of EPAC

3. EPAC1 is involved in chronic pain

3.1. Effects of EPAC1 on glial cells during pain

Glial cells in the nervous system provide nutritional support for neurons, wrap axons, and play an important role in the development and physiological function of the nervous system [40,41]. A large number of studies have shown that glial cells play an important role in the injury of the central nervous system, which will cause changes in morphology and microenvironment, secrete cytokines and inflammatory factors, and play an important role in the generation of chronic pain [41]. On top of that, it has been confirmed that peripheral glial cells play an important role in nociceptive information transmission as they are in response to nociceptive stimuli earlier than central glia and secrete inflammatory factors to push for further reaction [42,43].

3.1.1. Effects of EPAC1 on astrocytes

It is well known that activation of the astrocytes is closely related to pain. The chemotherapy-induced peripheral neuropathy (CIPN) is a major side effect of cancer treatment and can trigger neuroinflammation, producing intense pain that can seriously affect treatment effectiveness and patients' quality of life. Singhmar et al. found that EPAC1 knockout protected male and female mice from the effects of paclitaxel-induced mechanical allodynia, and pretreatment of EPAC competitive inhibitor, ESI-09 strongly inhibited the degree of mechanical allodynia. The chemotherapy drug paclitaxel causes sustained activation of stellar cells in normal mice, and ESI-09 normalizes the paclitaxel-induced overexpression of GFAP, a spinal cord stellar cell marker, which is not observed in EPAC1-deficient mice. In vitro cell experiments, cell-specific loss of EPAC1 in NaV1.8+ neurons also prevented paclitaxel from activating astrocytes. The high-frequency spontaneous discharge of DRG neurons induced by paclitaxel was inhibited by simultaneous administration of EPAC1 antagonist. In summary, EPAC1 inhibits astrocyte activation that induced by chemotherapy drugs and is expected to be a new target for treating CIPN [44].

3.1.2. Effects of EPAC1 on schwann cells

Schwann cells (SCs) are glial cells of the peripheral nervous system that form myelin sheaths, support axon integrity, and are essential for the function of neurons [45]. Paclitaxel induces the dedifferentiation of SCs and destroys their myelin formation ability, which may be closely related to the occurrence of CIPN. Phosphodiesterase 3 (PDE3) inhibitor cilostazol inhibited the degradation of cAMP accounting for increasing concentration of intracellular cAMP and the expression of myelin basic molecule, MBP meanwhile decreased the expression of low-affinity nerve growth factor p75, which contributed to the differentiation of SCs in mice. The effect of PDE3 on MBP and p75 can be inhibited by ESI-09. It can be concluded that cilostazol induces SCs differentiation by activating cAMP/EPAC signals and restrains CIPN caused by paclitaxel [46].

3.1.3. EPAC1 mediates pain through DRG neurons

DRG is susceptible to chemokines and leukocyte infiltration, thereby increasing the excitability of nociceptors, which promotes the occurrence and development of allodynia and hyperalgesia in DRG [47,48]. EPAC1 signaling pathways can enhance the excitability of receptive neurons in DRG. EPAC1-related PKC signaling can be activated by prostaglandin E2 (PGE2) receptor to enhance the hypersensitivity of nociceptors in DRG [49,50]. EPAC1 also can enhance capsaicin-induced secretion of calcitonin gene-related peptide from DRG neurons and activate EPAC/PKC signaling that enhances pain and ionic current induced by inflammatory response mediated by transient receptor potential vanilloid type 1 (TRPV1) in mouse and rat DRG [51,52]. Moreover, studies have confirmed that the expression level of EPAC1 may be the key to the transition from acute pain to chronic pain that occurs in DRG. In a glial cell-derived neurotrophic factor(GDNF)-induced mouse model of acute pain, inhibiting EPAC1 or increasing the GRK2 protein prevented this transition process [53]. Therefore, inhibition of the expression level of EPAC1 and its related pathways can affect sensory neurons and receptors in DRG and impact on pain processing.

3.2. Regulates key protein kinase of EPAC1

Protein kinases are involved in various physiological processes and signaling pathways in vivo, and conventional protein kinases are divided into eight groups based on sequence and functional homology [54]. As reviewed by Han in 2012, among the potential targets involved in the physiological pathology of pain, various protein kinases, such as PKA, PKC, and mitogen-activated protein kinase (MAPK), have now been identified as being associated with pain [55]. Several recent studies have shown that the interaction of EPAC1 with various protein kinases plays an important role in the occurrence and development of chronic pain.

3.2.1. PKA

PKA is responsible for the phosphorylation of many proteins, such as receptors, ion channels, transcription factors, etc., thereby regulating the biological activity response and balance in cells. A large number of studies have shown that PKA is involved in hyperalgesia [56]. cAMP acts as a secondary messenger for various physiological processes in the body, regulating cellular metabolism by activating PKA and targeting EPAC [57,58]. Both of them are cAMP sensors that mediate the cAMP response and can be activated individually or simultaneously. cAMP signaling has long been recognized as a major pathway for sensitization of nociceptors [59]. Therefore, in many pain responses, PKA and EPAC1 play a role together, and the two interact and act on other pathways, such as N-methyl-D-aspartic acid receptor (NMDAR). Latent sensitization is a sustainable form of sensitization mediated by adenylate cyclase (AC) and NMDA receptors that continues to function after the initial hyperalgesia subsides, contributing to the transition from acute pain to chronic pain. Peripheral inflammation can cause cAMP-dependent latent sensitization in the spinal cord, enhancing the severity and duration of pain. Further exploration of the cellular and molecular mechanisms of latent sensitization will help to deepen the understanding of chronic pain [60]. Studies have shown that EPAC is implicated in pain sensitization after inflammation or injury [61–63]. The neuropeptide tyrosine (NPY) and NPY Y1 receptor (Y1R) signaling cascade (called the NPY-Y1R axis) has an endogenous inhibitory effect on latent sensitization, and activation of this pathway can maintain pain relief. Activation of PKA and EPAC can increase the expression of dorsal horn pERK, a marker of central sensitization in persistent pain models in mice. The NPY-Y1R axis can maintain pain relief by inhibiting PKA and EPAC1/2 [64]. The drive of inflammation to latent sensitization can be realized through the NMDAR-AC1-EPAC1/2 pathway, and animal experiments have shown that compared with the NMDAR-AC1-PKA pathway, which only plays a role in latent sensitization of spinal dorsal horn in males, the former has no gender difference [64,65].

3.2.2. PKCε

PKC is a family of serine/threonine kinases consisting of 19 different isoenzymes divided into three subfamilies [66]. Among them, the ε isoform of protein kinase C, PKCε subtype is only found in the presynaptic terminal protein kinase of the small and medium DRG neuronal bodies and the traumatic neurons in the dorsal angle and has been found to play a role in inflammatory pain, neuropathic pain, and the transition from acute to chronic pain in mice and rats [67–69]. PKCε-specific inhibitors inhibited mechanical hyperalgesia induced by an EPAC-specific activator, the cAMP analog 8-(4-chlorophenylthio)-2′-O-methyl-cAMP (CPTOMe) in rats. EPAC was involved in epinephrin-induced PKCε-mediated hyperalgesia through the translocation and activation of PKCε mediated by phospholipase C (PLC) and PLD. The crosstalk between EPAC and PKCε is specific to small-diameter injury-inducing

neurons with isolectin B4(+) positive [IB4(+)], providing a novel cellular and molecular mechanism for therapeutic breakthroughs in inflammatory pain [70]. Wang et al. found that pretreatment of ESI-09 can reduce the expression of chronic morphine-induced purinergic receptor P2X3 (the main receptor for nociceptive information processing in DRG) and the phosphorylation of PKCε, showing anti-nociceptive tolerance against morphine induction in behavior of rats [71]. EPAC-dependent PKC activity has also been demonstrated in cell experiments in vitro, contributing to further understanding of the role of EPAC and PKCε crosstalk in chronic pain induced by nociceptor sensitization [72].

3.2.3. MAPK p38 ERK

The mitogen-activated protein kinase (MAPK) path has four main branches: ERK, JNK, p38 and ERK5. In a model of chronic postoperative pain (CPSP) established by plantar incisions, EPAC has been shown to maintain the activation of nociceptive receptors that cause the transition from acute pain to chronic pain. Pretreatment with ESI-09 significantly alleviated the duration and extent of persistent positive hypersensitivity induced by PGE. The mechanical hypersensitivity reaction time of rats pretreated with ESI-09 and p38 MAPK inhibitor, FR167653 was significantly shortened, and FR167653 greatly reduced the expression of EPAC1 in DRG caused by plantar incision injury. It is concluded that the increase of neuronal EPAC expression driven by p38MAPK activation is a key component leading to long-term nociceptive hypersensitivity after plantar incision. Therefore, the p38MAPK/EPAC pathway is a promising target for preventing the transition from acute pain to chronic pain [73]. A recent study on the reduction of postoperative hypersensitivity to pain with propofol in rats found that, compared with inhalation of isoflurane, propofol reduced postoperative hypersensitivity to pain by inhibiting the expression of phosphorylated GluN2B(p-GluN2B) in the spinal cord induced by plantar incision and the activity of its downstream molecule p38MAPK/EPAC1 pathway. The role of EPAC1 in pain provides a new idea for better understanding the mechanism of adjuvant drug use under general anesthesia [15].

3.2.4. GRK2

GRK2 is involved in the regulation of inflammatory hyperalgesia by influencing duration and severity [74,75]. Wang et al. found that mice with low GRK2 had significantly prolonged mechanical hyperalgesia after treatment with PGE and other cAMP inducers, and the interaction between EPAC1 and GRK2 could inhibit the downstream signal transduction of EPAC [53,76,77]. In recent studies, it has been shown that the initiation of hyperalgesia due to PGE in mice can be inhibited by subsequent up-regulation of GRK2 or down-regulation of EPAC1. The imbalance between EPAC1 and GRK2 is closely related to the prolongation of hyperalgesia, and maintaining the balance between EPAC1 and GRK2 provides a new idea for the prevention and treatment of chronic pain [78]. Pooja et al. further explored the mechanism by which GRK2 controls EPAC1-mediated pain signaling in the mouse CFA model, finding that GRK2 mediates the phosphorylation of Ser-108 in EPAC1 to the serine/threonine or tyrosine residue of the hydroxyl transferase of the target protein, leading to regulation of the activity of EPAC1 [79].

3.3. Ion channel

Ion channels and transporters are key mediators of nociceptive pain. We provide updated information on ion channels that may be involved in mediating nociceptive pathways associated with EPAC1-mediated chronic pain, including Piezo channel 2(Piezo2),caveolin-1(Cav-1), transient receptor potential (TRP) channel, and purinergic receptor complexes [80].

3.3.1. EPAC1-Piezo2

Piezo2 has been identified in recent studies as an ion channel involved in mechanical hyperalgesia and abnormal pain, such as osteoarthritis [81] and visceral hypersensitivity [82]. Eijkelkamp et al. used L5 spinal nerve ligation (SNL) to establish a model of chronic neuropathic pain in which EPAC1 knockout mice experienced significant relief from abnormal pain compared to wild-type mice. The EPAC-specific agonist, 8-pCPT enhances Piezo2-mediated mechanical transduction in low-threshold mechanosensitive sensory neurons in cells, thereby promoting the development of abnormal pain, but whether EPAC1 directly or indirectly acts on Piezo2 remains to be further explored. Studies have shown that the EPAC1-Piezo2 axis is an important regulator of abnormal pain and a promising target for the treatment of neuropathic pain [83].

3.3.2. EPAC1-Cav1

In a rat model of CPSP established by plantar incisions, EPAC has been shown to maintain the activation of nociceptive receptors that cause the transition from acute pain to chronic pain. Hua et al. found that blocking EPAC1 can reverse CPSP induced by the Skin/Muscle Incision and Retraction (SMIR) model by inhibiting the overexpression of Cav-1 [84]. Cav-1 has been shown to regulate cellular endocytosis and vesicular transport, contributing to hippocampal synapses and neuroplasticity in mice [85]. Previous studies have found that Cav-1 expression in the spinal cord is consistently upregulated and promotes mechanical hyperalgesia in rats with nerve injury [86]. Therefore, it can be inferred that EPAC1-Cav1 is a possible mechanism of CPSP. Inhibition of EPAC1 has also been shown to alleviate CPSP by inhibiting astrocyte activation [87].

3.3.3. TRPA1-AC1-EPAC

Diabetic peripheral neuropathic pain (DPNP) is associated with increased methylethylene glycol (MG) levels and decreased expression and activity of the major MG detoxification enzyme glyoxal-1 (GLO1) [88]. Studies have shown that intrathecal injection of AC inhibitor, SQ22536 can alleviate mechanical hyperalgesia and thermal sensitivity in type 2 diabetic rats [89]. Ryan B and colleagues established a db/db mouse model of type 2 diabetes in which intrathecal administration of transient receptor potential A1(TRPA1), AC1, and EPAC1/2 inhibitors reversed MG-induced mechanical hypersensitivity and thermal sensitivity. The role of spinal cord TRPA1-AC1-EPAC cascade in neuropathic pain induced by type 2 diabetes was determined [90].

3.3.4. P2Rs-cAMP-EPAC1

Luo and colleagues found that the cAMP-EPAC1 signaling pathway is activated after chronic compression of the trigeminal nerve root in rats, and nerve injury releases adenosine-triphosphate (ATP) to activate purinergic 2 receptors (P2Rs) and cAMP pathway on the cell membrane, both of which can participate in the transduction of pain signals [91,92].

3.4. Mitochondrial dysfunction

cAMP is a major regulator of mitochondrial metabolism, and its benefits are reflected in many aspects, including but not limited to, protecting the liver from the liver toxicity of some drugs [93], regulating pain response [94], and inhibiting tumor growth [95]. The potential contribution of mitochondrial dysfunction in hyperalgesia has aroused strong interest of researchers [54–56]. cAMP-mediated activation of EPAC1 contributes to translocation of EPAC1 to the plasma membrane and activation of Rap1 and other downstream [16,96]. Activated PKCε translocates to mitochondria where it reduces complex I respiration and Na^+-K^+-ATPase activity, which may lead to mitochondrial insufficiency [97]. In addition, EPAC1-Rap1 signaling can maintain homeostasis of mitochondrial dynamics and inhibit mitochondria-mediated apoptosis by regulating the expression of mitochondrial fission protein, Drp1 and mitochondrial fusion-related protein, MFN2. Another study demonstrated that the protective effect of EPAC1-deficient mice against paclitaxel-induced mechanical pain may be related to the preservation of mitochondrial function in mice [44]. Inhibition of EPAC1 may be a

potentially effective therapeutic strategy for the prevention and treatment of pre-existing paclitaxel-induced neuropathy, however the specific mechanism by which EPAC1 activation leads to mitochondrial defects, and whether there is a cAMP-dependent mechanism, remains to be determined.

3.5. Mechanism of endothelial permeability

EPAC1 can partially control cell adhesion and regulate the endothelial permeability barrier under injury, and plays a role in maintaining endothelial integrity and permeability [98,99]. Pan and colleagues have shown that macrophages and endothelial cells are functionally coupled through EPAC1-P120 and can reshape nociceptors through macrophages, endothelial cells and their side pathways in inflammation and microenvironment in rat postoperative chronic pain models which may be a key step in the transition of acute pain to CPSP [100]. To evaluate the expression of P120 and EPAC1 in the muscle tissue around the incision may be used as markers of CPSP.

4. Conclusion

Since the 1980s, the research of EPAC protein has made a lot of progress, but there are still many deficiencies in the aspects of pain, especially chronic pain. Changes in signaling pathways and molecular mechanisms involved in the activation of EPAC1 such as protein kinase and Ion channel play an integral role in the progression and maintenance of chronic pain (Fig. 2). However, more relationships with glial cells remain to be explored, and the interaction between EPAC and mitochondria in pain also remain unclear. Elucidating the underlying mechanism of EPAC1 activation is of great significance to the research and treatment of chronic pain management in the world. Currently, it is particularly important for entirely new targeted pain treatments after an over-reliance on opioids. It is believed that there will be greater breakthroughs in the research progress of EPAC1 in chronic pain, making it a new intervention for the treatment of chronic pain.

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CRediT authorship contribution statement

Chenlu Jiang: Writing – original draft. **Jiacheng Zhao:** Writing – review & editing. **Yihang Zhang:** Writing – original draft. **Xiang Zhu:** Supervision.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

Abbreviations

EPAC	the exchange protein directly activated by Camp
cAMP	cyclic adenosine monophosphate
Ras	rat sarcoma
PKA	protein kinase A
CFA	complete Freund's adjuvant
PKC	protein kinase C
GRK2	G protein coupled receptor kinase 2 ()
CNB	cyclic nucleotide binding
DEP	dishevelled–EGL–pleckstrin homology domain
REM	Ras exchange motif
RA	Ras-associated
CDC25HD	CDC25 homology domain
apo	unbound EPAC
Rap-1	Ras-related protein-1
DRG	dorsal root ganglion
LPS	lipopolysaccharide
CIPN	chemotherapy-induced peripheral neuropathy
SCs	Schwann cells
PDE3	phosphodiesterase 3
PGE2	prostaglandin E2
TRPV1	transient receptor potential vanilloid type 1
GDNF	glial cell-derived neurotrophic factor
MAPK	mitogen-activated protein kinase
NMDAR	N-methyl-D-aspartic acid receptor

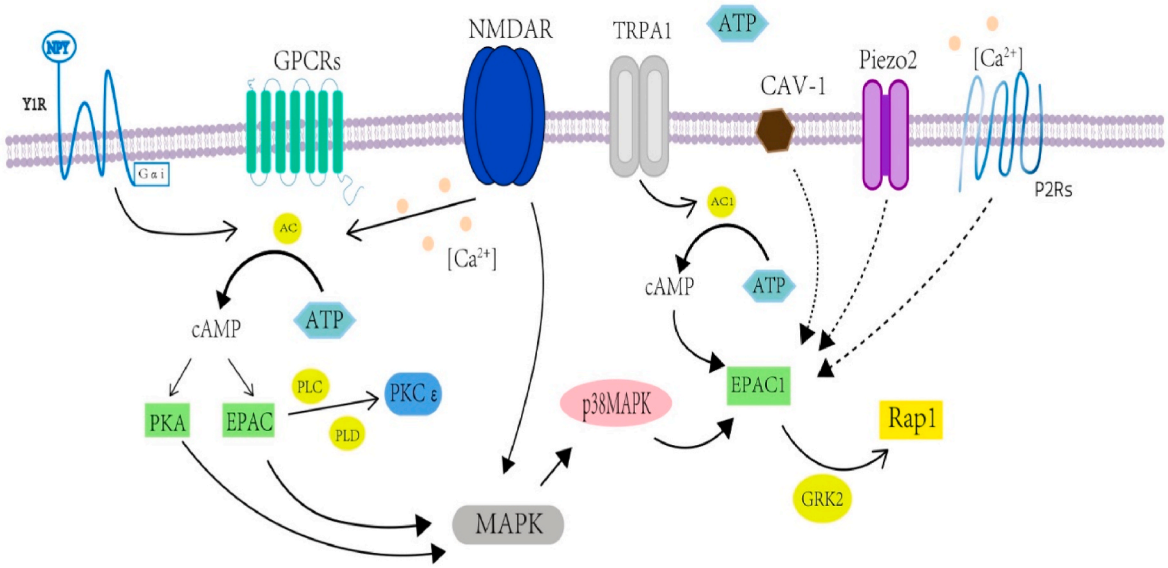

Fig. 2. The potential mechanism of EPAC1 pathway in chronic pain development.

AC	adenylate cyclase
NPY	neuropeptide tyrosine
Y1R	NPY Y1 receptor
CPTOMe	the cAMP analog 8-(4-chlorophenylthio)-2′-O-methyl-cAMP
PLC	phospholipase C
PLD	phospholipase D
IB4	isolectin B4
MAPK	mitogen-activated protein kinase
CPSP	chronic postoperative pain
p-GluN2B	phosphorylated GluN2B
Piezo2	Piezo channel 2
Cav-1	caveolin-1
TRPA1	transient receptor potential A1
SNL	spinal nerve ligation
SMIR	Skin/Muscle Incision and Retraction
DPNP	diabetic peripheral neuropathic pain
MG	methylethylene glycol
GLO1	glyoxal-1
ATP	adenosine-triphosphate
P2Rs	purinergic 2 receptors

References

[1] T. Li, X. Chen, C. Zhang, Y. Zhang, W. Yao, An update on reactive astrocytes in chronic pain, J. Neuroinflammation 16 (1) (2019) 140.

[2] T. Nakagawa, S. Kaneko, Spinal astrocytes as therapeutic targets for pathological pain, J. Pharmacol. Sci. 114 (4) (2010) 347–353.

[3] R.R. Ji, A. Nackley, Y. Huh, N. Terrando, W. Maixner, Neuroinflammation and central sensitization in chronic and widespread pain, Anesthesiology 129 (2) (2018) 343–366.

[4] W.G. Robichaux 3rd, X. Cheng, Intracellular cAMP sensor EPAC: physiology, pathophysiology, and therapeutics development, Physiol. Rev. 98 (2) (2018) 919–1053.

[5] Y. Sakai, M. Tsunekawa, K. Ohta, T. Shimizu, St Pastuhov, H. Hanafusa, N. Hisamoto, K. Matsumoto, The integrin signaling network promotes axon regeneration via the src-ephexin-RhoA GTPase signaling Axis, J. Neurosci. 41 (22) (2021) 4754–4767.

[6] A. Tengholm, E. Gylfe, cAMP signalling in insulin and glucagon secretion, Diabetes Obes. Metabol. 19 (Suppl 1) (2017) 42–53.

[7] F. Zou, Y. Li, S. Zhang, J. Zhang, DP1 (prostaglandin D(2) receptor 1) activation protects against vascular remodeling and vascular smooth muscle cell transition to myofibroblasts in angiotensin II-induced hypertension in mice, Hypertension 79 (6) (2022) 1203–1215.

[8] S.C. Berkey, J.J. Herrera, M.A. Odem, S. Rahman, S.S. Cheruvu, X. Cheng, E. T. Walters, C.W. Dessauer, A.G. Bavencoffe, EPAC1 and EPAC2 promote nociceptor hyperactivity associated with chronic pain after spinal cord injury, Neurobiol Pain 7 (2020) 100040.

[9] Y. Gu, G. Li, L.M. Huang, Inflammation induces Epac-protein kinase C alpha and epsilon signaling in TRPV1-mediated hyperalgesia, Pain 159 (11) (2018) 2383–2393.

[10] C. Wang, Y. Gu, G.W. Li, L.Y. Huang, A critical role of the cAMP sensor Epac in switching protein kinase signalling in prostaglandin E2-induced potentiation of P2X3 receptor currents in inflamed rats, J. Physiol. 584 (Pt 1) (2007) 191–203.

[11] R.B. Griggs, D.F. Santos, D.E. Laird, S. Doolen, R.R. Donahue, C.R. Wessel, W. Fu, G.P. Sinha, P. Wang, J. Zhou, et al., Methylglyoxal and a spinal TRPA1-AC1-Epac cascade facilitate pain in the db/db mouse model of type 2 diabetes, Neurobiol. Dis. 127 (2019) 76–86.

[12] W. Li, C. Qin, J. Yan, Q. Zhao, L. You, Y. Yang, Propofol alleviates neuropathic pain induced by chronic contractile injury by regulating the spinal glun2b-p38mapkepac1 pathway, Comput. Math. Methods Med. (2021) 9305076.

[13] S. Cao, Z. Bian, X. Zhu, S.R. Shen, Effect of Epac1 on pERK and VEGF activation in postoperative persistent pain in rats, J. Mol. Neurosci. 59 (4) (2016) 554–564.

[14] J. Qian, X. Lin, Z. Zhou, Skin/muscle incision and retraction regulates the persistent postoperative pain in rats by the Epac1/PKC-betaII pathway, BMC Anesthesiol. 22 (1) (2022) 230.

[15] S.S. Wong, L. Sun, Q. Qiu, P. Gu, Q. Li, X.M. Wang, C.W. Cheung, Propofol attenuates postoperative hyperalgesia via regulating spinal GluN2B-p38MAPK/EPAC1 pathway in an animal model of postoperative pain, Eur. J. Pain 23 (4) (2019) 812–822.

[16] T.B. Hucho, O.A. Dina, J.D. Levine, Epac mediates a cAMP-to-PKC signaling in inflammatory pain: an isolectin B4(+) neuron-specific mechanism, J. Neurosci. 25 (26) (2005) 6119–6126.

[17] X.H. Xu, R.Q. Du, L. Li, L.L. Yang, Y. Zhang, Q.M. Li, The role of G-protein-coupled receptor kinase 2 in diabetic mechanical hyperalgesia in rats, Eur. J. Pain 25 (9) (2021) 2039–2049.

[18] S.C. Berkey, J.J. Herrera, M.A. Odem, S. Rahman, S.S. Cheruvu, X. Cheng, E. T. Walters, C.W. Dessauer, A.G. Bavencoffe, EPAC1 and EPAC2 promote nociceptor hyperactivity associated with chronic pain after spinal cord injury, Neurobiol Pain 7 (2020) 100040.

[19] J.L. Bos, Epac: a new cAMP target and new avenues in cAMP research, Nat. Rev. Mol. Cell Biol. 4 (9) (2003) 733–738.

[20] J. de Rooij, F.J. Zwartkruis, M.H. Verheijen, R.H. Cool, S.M. Nijman, A. Wittinghofer, J.L. Bos, Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP, Nature 396 (6710) (1998) 474–477.

[21] H. Mohamed, H. Shao, M. Akimoto, P. Darveau, M.R. MacKinnon, J. Magolan, G. Melacini, QSAR models reveal new EPAC-selective allosteric modulators, RSC Chem Biol 3 (10) (2022) 1230–1239.

[22] J. de Rooij, H. Rehmann, M. van Triest, R.H. Cool, A. Wittinghofer, J.L. Bos, Mechanism of regulation of the Epac family of cAMP-dependent RapGEFs, J. Biol. Chem. 275 (27) (2000) 20829–20836.

[23] B. Ponsioen, M. Gloerich, L. Ritsma, H. Rehmann, J.L. Bos, K. Jalink, Direct spatial control of Epac1 by cyclic AMP, Mol. Cell Biol. 29 (10) (2009) 2521–2531.

[24] A.G. Peace, D.A. Shewan, New perspectives in cyclic AMP-mediated axon growth and guidance: the emerging epoch of Epac, Brain Res. Bull. 84 (4–5) (2011) 280–288.

[25] J. Lee, J. Park, J.H. Kim, G. Lee, T.E. Park, K.J. Yoon, Y.K. Kim, C. Lim, LSM12-EPAC1 defines a neuroprotective pathway that sustains the nucleocytoplasmic RAN gradient, PLoS Biol. 18 (12) (2020) e3001002.

[26] A. Guijarro-Belmar, D.M. Domanski, X. Bo, D. Shewan, W. Huang, The therapeutic potential of targeting exchange protein directly activated by cyclic adenosine 3',5'-monophosphate (Epac) for central nervous system trauma, Neural Regen Res 16 (3) (2021) 460–469.

[27] Z.Z. Gao, Y.C. Li, C.Y. Shao, J. Xiao, Y. Shen, L. Zhou, EPAC negatively regulates myelination via controlling proliferation of oligodendrocyte precursor cells, Neurosci. Bull. 36 (6) (2020) 639–648.

[28] X. Sun, Y. Wang, Y. Zhao, X. Xu, W. Lu, Y. Li, F. Bian, L. Xiang, L. Zhou, Activation of the Epac/Rap1 signaling pathway alleviates blood-brain barrier disruption and brain damage following cerebral ischemia/reperfusion injury, Int. Immunopharm. 117 (2023) 110014.

[29] X.T. Wang, L. Zhou, B.B. Dong, F.X. Xu, D.J. Wang, E.W. Shen, X.Y. Cai, Y. Wang, N. Wang, S.J. Ji, et al., cAMP-EPAC-PKCepsilon-RIM1alpha signaling regulates presynaptic long-term potentiation and motor learning, Elife (2023) 12.

[30] N. Kakogiannos, L. Ferrari, C. Giampietro, A.A. Scalise, C. Maderna, M. Rava, A. Taddei, M.G. Lampugnani, F. Pisati, M. Malinverno, et al., JAM-A acts via C/EBP-alpha to promote claudin-5 expression and enhance endothelial barrier function, Circ. Res. 127 (8) (2020) 1056–1073.

[31] W. Chu, X. Sun, X. Zhu, Y.C. Zhao, J. Zhang, Q. Kong, L. Zhou, Blockade of platelet glycoprotein receptor Ib ameliorates blood-brain barrier disruption following ischemic stroke via Epac pathway, Biomed. Pharmacother. 140 (2021) 111698.

[32] A.J. Murray, D.A. Shewan, Epac mediates cyclic AMP-dependent axon growth, guidance and regeneration Mol Cell Neurosci 38 (4) (2008) 578–588.

[33] A.J. Murray, S.J. Tucker, D.A. Shewan, cAMP-dependent axon guidance is distinctly regulated by Epac and protein kinase A, J. Neurosci. 29 (49) (2009) 15434–15444.

[34] H.J. Yang, A. Vainshtein, G. Maik-Rachline, E. Peles, G protein-coupled receptor 37 is a negative regulator of oligodendrocyte differentiation and myelination, Nat. Commun. 7 (2016) 10884.

[35] Q. Zhong, H. Yu, C. Huang, J. Zhong, H. Wang, J. Xu, Y. Cheng, FCPR16, a novel phosphodiesterase 4 inhibitor, produces an antidepressant-like effect in mice exposed to chronic unpredictable mild stress, Prog. Neuro-Psychopharmacol. Biol. Psychiatry 90 (2019) 62–75.

[36] Q. Wang, X. Dong, T. Hu, C. Qu, J. Lu, Y. Zhou, J. Li, G. Pei, Constitutive activity of serotonin receptor 6 regulates human cerebral organoids formation and depression-like behaviors, Stem Cell Rep. 16 (1) (2021) 75–88.

[37] N.T. Fiore, S.R. Debs, J.P. Hayes, S.S. Duffy, G. Moalem-Taylor, Pain-resolving immune mechanisms in neuropathic pain, Nat. Rev. Neurol. 19 (4) (2023) 199–220.

[38] E.E. Putnins, V. Goebeler, M. Ostadkarampour, Monoamine oxidase-B inhibitor reduction in pro-inflammatory cytokines mediated by inhibition of cAMP-PKA/EPAC signaling, Front. Pharmacol. 12 (2021) 741460.

[39] N. Musheshe, A. Oun, A.M. Sabogal-Guaqueta, M. Trombetta-Lima, S.C. Mitchel, A. Adzemovic, O. Speek, F. Morra, C. van der Veen, F. Lezoualc'h, et al., Pharmacological inhibition of Epac1 averts ferroptosis cell death by preserving mitochondrial integrity, Antioxidants 11 (2) (2022).

[40] M.R. Freeman, Specification and morphogenesis of astrocytes, Science 330 (6005) (2010) 774–778.

[41] R.R. Ji, A. Chamessian, Y.Q. Zhang, Pain regulation by non-neuronal cells and inflammation, Science 354 (6312) (2016) 572–577.

[42] M. Calvo, J.M. Dawes, D.L. Bennett, The role of the immune system in the generation of neuropathic pain, Lancet Neurol. 11 (7) (2012) 629–642.

[43] H. Abdo, L. Calvo-Enrique, J.M. Lopez, J. Song, M.D. Zhang, D. Usoskin, A. El Manira, I. Adameyko, J. Hjerling-Leffler, P. Ernfors, Specialized cutaneous Schwann cells initiate pain sensation, Science 365 (6454) (2019) 695–699.

[44] P. Singhmar, X. Huo, Y. Li, P.M. Dougherty, F. Mei, X. Cheng, C.J. Heijnen, A. Kavelaars, Orally active Epac inhibitor reverses mechanical allodynia and loss of intraepidermal nerve fibers in a mouse model of chemotherapy-induced peripheral neuropathy, Pain 159 (5) (2018) 884–893.

[45] G. Nocera, C. Jacob, Mechanisms of Schwann cell plasticity involved in peripheral nerve repair after injury, Cell. Mol. Life Sci. 77 (20) (2020) 3977–3989.

[46] M. Koyanagi, S. Imai, Y. Iwamitsu, M. Matsumoto, M. Saigo, A. Moriya, T. Ogihara, Y. Nakazato, A. Yonezawa, S. Nakagawa, et al., Cilostazol is an effective causal therapy for preventing paclitaxel-induced peripheral neuropathy by suppression of Schwann cell dedifferentiation, Neuropharmacology 188 (2021) 108514.

[47] S. Huang, C.G.K. Ziegler, J. Austin, N. Mannoun, M. Vukovic, J. Ordovas-Montanes, A.K. Shalek, U.H. von Andrian, Lymph nodes are innervated by a unique population of sensory neurons with immunomodulatory potential, Cell 184 (2) (2021) 441–459 e425.
[48] D. Guha, M.F. Shamji, The dorsal root ganglion in the pathogenesis of chronic neuropathic pain, Neurosurgery 63 (Suppl 1) (2016) 118–126.
[49] W. Ma, B. St-Jacques, Signalling transduction events involved in agonist-induced PGE2/EP4 receptor externalization in cultured rat dorsal root ganglion neurons, Eur. J. Pain 22 (5) (2018) 845–861.
[50] U. Yokoyama, K. Iwatsubo, M. Umemura, T. Fujita, Y. Ishikawa, The prostanoid EP4 receptor and its signaling pathway, Pharmacol. Rev. 65 (3) (2013) 1010–1052.
[51] K. Schnizler, L.P. Shutov, M.J. Van Kanegan, M.A. Merrill, B. Nichols, G. S. McKnight, S. Strack, J.W. Hell, Y.M. Usachev, Protein kinase A anchoring via AKAP150 is essential for TRPV1 modulation by forskolin and prostaglandin E2 in mouse sensory neurons, J. Neurosci. 28 (19) (2008) 4904–4917.
[52] Y. Gu, G. Li, L.M. Huang, Inflammation induces Epac-protein kinase C alpha and epsilon signaling in TRPV1-mediated hyperalgesia, Pain 159 (11) (2018) 2383–2393.
[53] H.J. Wang, H.X. Gu, N. Eijkelkamp, C.J. Heijnen, A. Kavelaars, Low GRK2 underlies hyperalgesic priming by glial cell-derived neurotrophic factor, Front. Pharmacol. 9 (2018) 592.
[54] F. Giraud, E. Pereira, F. Anizon, P. Moreau, Recent advances in pain management: relevant protein kinases and their inhibitors, Molecules 26 (9) (2021).
[55] H. Han, K.S. Lee, W. Rong, G. Zhang, Different roles of peripheral mitogen-activated protein kinases in carrageenan-induced arthritic pain and arthritis in rats, Anesth. Analg. 115 (5) (2012) 1221–1227.
[56] M. Grandoch, S.S. Roscioni, M. Schmidt, The role of Epac proteins, novel cAMP mediators, in the regulation of immune, lung and neuronal function, Br. J. Pharmacol. 159 (2) (2010) 265–284.
[57] H. Kawasaki, G.M. Springett, N. Mochizuki, S. Toki, M. Nakaya, M. Matsuda, D. E. Housman, A.M. Graybiel, A family of cAMP-binding proteins that directly activate Rap1, Science 282 (5397) (1998) 2275–2279.
[58] B. Weinhold, N. Amrhein, Activation of rabbit skeletal muscle adenosine-3':5'-monophosphate-dependent protein kinase by agitation, Biochem. Biophys. Res. Commun. 76 (4) (1977) 1116–1123.
[59] S.H. Ferreira, M. Nakamura, I - prostaglandin hyperalgesia, a cAMP/Ca2+ dependent process, Prostaglandins 18 (2) (1979) 179–190.
[60] M. Gerum, F. Simonin, Behavioral characterization, potential clinical relevance and mechanisms of latent pain sensitization, Pharmacol. Ther. 233 (2022) 108032.
[61] A. Garza Carbajal, A. Ebersberger, A. Thiel, L. Ferrari, J. Acuna, S. Brosig, J. Isensee, K. Moeller, M. Siobal, S. Rose-John, et al., Oncostatin M induces hyperalgesic priming and amplifies signaling of cAMP to ERK by RapGEF2 and PKA, J. Neurochem. (6) (2021) 1821–1837.
[62] S.T. Huang, B.B. Chen, Z.J. Song, H.L. Tang, R. Hua, Y.M. Zhang, Unraveling the role of Epac1-SOCS3 signaling in the development of neonatal-CRD-induced visceral hypersensitivity in rats, CNS Neurosci. Ther. 28 (9) (2022) 1393–1408.
[63] L.Y. Huang, Y. Gu, Epac and nociceptor sensitization, Mol. Pain 1744806917716234 (2017).
[64] W. Fu, T.S. Nelson, D.F. Santos, S. Doolen, J.J.P. Gutierrez, N. Ye, J. Zhou, B KT: an NPY Y1 receptor antagonist unmasks latent sensitization and reveals the contribution of protein kinase A and Epac to chronic inflammatory pain, Pain 160 (8) (2019) 1754–1765.
[65] P. Basu, L. Custodio-Patsey, P. Prasoon, B.N. Smith, B.K. Taylor, Sex differences in protein kinase A signaling of the latent postoperative pain sensitization that is masked by kappa opioid receptors in the spinal cord, J. Neurosci. (47) (2021) 9827–9843.
[66] Y. Nishizuka, The molecular heterogeneity of protein kinase C and its implications for cellular regulation, Nature 334 (6184) (1988) 661–665.
[67] X. Zhao, B. Xia, J. Cheng, M.X. Zhu, Y. Li, PKCepsilon SUMOylation is required for mediating the nociceptive signaling of inflammatory pain, Cell Rep. 33 (1) (2020) 108191.
[68] J. Fang, S. Wang, J. Zhou, X. Shao, H. Sun, Y. Liang, X. He, Y. Jiang, B. Liu, X. Jin, et al., Electroacupuncture regulates pain transition through inhibiting PKCepsilon and TRPV1 expression in dorsal root ganglion, Front. Neurosci. 15 (2021) 685715.
[69] J. Xu, S. Wu, J. Wang, J. Wang, Y. Yan, M. Zhu, D. Zhang, C. Jiang, T. Liu, Oxidative stress induced by NOX2 contributes to neuropathic pain via plasma membrane translocation of PKCepsilon in rat dorsal root ganglion neurons, J. Neuroinflammation 18 (1) (2021) 106.
[70] T.B. Hucho, O.A. Dina, J.D. Levine, Epac mediates a cAMP-to-PKC signaling in inflammatory pain: an isolectin B4(+) neuron-specific mechanism, J. Neurosci. (26) (2005) 6119–6126.
[71] W. Wang, X. Ma, L. Luo, M. Huang, J. Dong, X. Zhang, W. Jiang, T. Xu, Exchange factor directly activated by cAMP-PKCepsilon signalling mediates chronic morphine-induced expression of purine P2X3 receptor in rat dorsal root ganglia, Br. J. Pharmacol. 175 (10) (2018) 1760–1769.
[72] D.J. Goode, D.C. Molliver, Phospho-substrate profiling of Epac-dependent protein kinase C activity, Mol. Cell. Biochem. 456 (1–2) (2019) 167–178.
[73] M. Matsuda, K. Oh-Hashi, I. Yokota, T. Sawa, F. Amaya, Acquired exchange protein directly activated by cyclic adenosine monophosphate activity induced by p38 mitogen-activated protein kinase in primary afferent neurons contributes to sustaining postincisional nociception, Anesthesiology 126 (1) (2017) 150–162.
[74] N. Eijkelkamp, C.J. Heijnen, H.L. Willemen, R. Deumens, E.A. Joosten, W. Kleibeuker, I.J. den Hartog, C.T. van Velthoven, C. Nijboer, M.A. Nassar, et al., GRK2: a novel cell-specific regulator of severity and duration of inflammatory pain, J. Neurosci. 30 (6) (2010) 2138–2149.
[75] L.F. Ferrari, O. Bogen, N. Alessandri-Haber, E. Levine, R.W. Gear, J.D. Levine, Transient decrease in nociceptor GRK2 expression produces long-term enhancement in inflammatory pain, Neuroscience 222 (2012) 392–403.
[76] N. Eijkelkamp, H. Wang, A. Garza-Carbajal, H.L. Willemen, F.J. Zwartkruis, J. N. Wood, R. Dantzer, K.W. Kelley, C.J. Heijnen, A. Kavelaars, Low nociceptor GRK2 prolongs prostaglandin E2 hyperalgesia via biased cAMP signaling to Epac/Rap1, protein kinase Cepsilon, and MEK/ERK, J. Neurosci. 30 (38) (2010) 12806–12815.
[77] H. Wang, C.J. Heijnen, N. Eijkelkamp, A.G. Carbajal, M. Schedlowski, K. W. Kelley, R. Dantzer, A. Kavelaars, GRK2 in sensory neurons regulates epinephrine-induced signalling and duration of mechanical hyperalgesia, Pain 152 (7) (2011) 1649–1658.
[78] H. Wang, C.J. Heijnen, C.T. van Velthoven, H.L. Willemen, Y. Ishikawa, X. Zhang, A.K. Sood, A. Vroon, N. Eijkelkamp, A. Kavelaars, Balancing GRK2 and EPAC1 levels prevents and relieves chronic pain, J. Clin. Invest. 123 (12) (2013) 5023–5034.
[79] P. Singhmar, X. Huo, N. Eijkelkamp, S.R. Berciano, F. Baameur, F.C. Mei, Y. Zhu, X. Cheng, D. Hawke, F. Mayor Jr., et al., Critical role for Epac1 in inflammatory pain controlled by GRK2-mediated phosphorylation of Epac1, Proc. Natl. Acad. Sci. U. S. A. 113 (11) (2016) 3036–3041.
[80] C. Matta, R. Takacs, L. Ducza, R.A. Ebeid, H. Choi, A. Mobasheri, Ion channels involved in inflammation and pain in osteoarthritis and related musculoskeletal disorders, Am. J. Physiol. Cell Physiol. 325 (1) (2023) C257–C271.
[81] A.M. Obeidat, M.J. Wood, N.S. Adamczyk, S. Ishihara, J. Li, L. Wang, D. Ren, D. A. Bennett, R.J. Miller, A.M. Malfait, et al., Piezo2 expressing nociceptors mediate mechanical sensitization in experimental osteoarthritis, Nat. Commun. 14 (1) (2023) 2479.
[82] J. Xu, A. McGinnis, R.R. Ji, Piezo2 mediates visceral mechanosensation: a new therapeutic target for gut pain? Neuron 111 (4) (2023) 450–452.
[83] N. Eijkelkamp, J.E. Linley, J.M. Torres, L. Bee, A.H. Dickenson, M. Gringhuis, M. S. Minett, G.S. Hong, E. Lee, U. Oh, et al., A role for Piezo2 in EPAC1-dependent mechanical allodynia, Nat. Commun. 4 (2013) 1682.
[84] Q. Hua, S. Shen, Y. Qin, S. Cao, CAV-1 overexpression exacerbates the manifestation in EPAC-1-induced chronic postsurgical pain in rats, Pain Res. Manag. 2022 (2022) 8566840.
[85] S. Wang, T. Ichinomiya, P. Savchenko, D. Wang, A. Sawada, X. Li, T. Duong, W. Li, J.A. Bonds, E.J. Kim, et al., Subpial delivery of adeno-associated virus 9-synapsin-caveolin-1 (AAV9-SynCav1) preserves motor neuron and neuromuscular junction morphology, motor function, delays disease onset, and extends survival in hSOD1(G93A) mice, Theranostics 12 (12) (2022) 5389–5403.
[86] G.L. Jia, Q. Huang, Y.N. Cao, C.S. Xie, Y.J. Shen, J.L. Chen, J.H. Lu, M.B. Zhang, J. Li, Y.X. Tao, et al., Cav-1 participates in the development of diabetic neuropathy pain through the TLR4 signaling pathway, J. Cell. Physiol. 235 (3) (2020) 2060–2070.
[87] Q. She, J. Chen, C. Zhong, S. Huang, C. Lu, Y. Qin, Exchange proteins directly activated by cyclic adenosine monophosphate inhibitor reverses mechanical allodynia via the modification of astrocytes activity in the spinal cord, Ann. Transl. Med. 9 (22) (2021) 1656.
[88] N.F. Abdelkader, S.M. Ibrahim, P.E. Moustafa, M.A. Elbaset, Inosine mitigated diabetic peripheral neuropathy via modulating GLO1/AGEs/RAGE/NF-kappaB/Nrf2 and TGF-beta/PKC/TRPV1 signaling pathways, Biomed. Pharmacother. 145 (2022) 112395.
[89] H. Feng, G. Lu, Q. Li, Z. Liu, Inhibition of adenylyl cyclase in the spinal cord alleviates painful diabetic neuropathy in zucker diabetic fatty rats, Can. J. Diabetes 41 (2) (2017) 177–183.
[90] R.B. Griggs, D.F. Santos, D.E. Laird, S. Doolen, R.R. Donahue, C.R. Wessel, W. Fu, G.P. Sinha, P. Wang, J. Zhou, et al., Methylglyoxal and a spinal TRPA1-AC1-Epac cascade facilitate pain in the db/db mouse model of type 2 diabetes, Neurobiol. Dis. 127 (2019) 76–86.
[91] K. Inoue, M. Tsuda, Nociceptive signaling mediated by P2X3, P2X4 and P2X7 receptors, Biochem. Pharmacol. 187 (2021) 114309.
[92] Z. Luo, X. Liao, L. Luo, Q. Fan, X. Zhang, Y. Guo, F. Wang, Z. Ye, D. Luo, Extracellular ATP and cAMP signaling promote Piezo2-dependent mechanical allodynia after trigeminal nerve compression injury, J. Neurochem. 160 (3) (2022) 376–391.
[93] F.A.A. Mora, N. Musheshe, J.C. Arroyave Ospina, Y. Geng, J.M. Soto, J. A. Rodrigo, T. Alieva, M. Buist-Homan, F. Lezoualc'h, X. Cheng, et al., Metformin protects against diclofenac-induced toxicity in primary rat hepatocytes by preserving mitochondrial integrity via a pathway involving EPAC, Biomed. Pharmacother. 143 (2021) 112072.
[94] A. Garza Carbajal, A. Bavencoffe, E.T. Walters, C.W. Dessauer, Depolarization-dependent C-Raf signaling promotes hyperexcitability and reduces opioid sensitivity of isolated nociceptors after spinal cord injury, J. Neurosci. 40 (34) (2020) 6522–6535.
[95] Y. Maeda, R. Kikuchi, J. Kawagoe, T. Tsuji, N. Koyama, K. Yamaguchi, H. Nakamura, K. Aoshiba, Anti-cancer strategy targeting the energy metabolism of tumor cells surviving a low-nutrient acidic microenvironment, Mol. Metabol. 42 (2020) 101093.
[96] S.V. Consonni, M. Gloerich, E. Spanjaard, J.L. Bos, cAMP regulates DEP domain-mediated binding of the guanine nucleotide exchange factor Epac1 to phosphatidic acid at the plasma membrane, Proc. Natl. Acad. Sci. U. S. A. 109 (10) (2012) 3814–3819.

[97] G. Nowak, D. Bakajsova, G.L. Clifton, Protein kinase C-epsilon modulates mitochondrial function and active Na+ transport after oxidant injury in renal cells, Am. J. Physiol. Ren. Physiol. 286 (2) (2004) F307–F316.
[98] J.L. Bos, Epac proteins: multi-purpose cAMP targets, Trends Biochem. Sci. 31 (12) (2006) 680–686.
[99] Y. Gu, G. Li, Y. Chen, L.M. Huang, Epac-protein kinase C alpha signaling in purinergic P2X3R-mediated hyperalgesia after inflammation, Pain 157 (7) (2016) 1541–1550.
[100] P. Pan, S.S. Huang, S.R. Shen, C.E. Lu, Y.B. Qin, J.L. Zhang, S. Cao, Role of p120 catenin in Epac1-induced chronic postsurgical pain in rats, Pain Res. Manag. 2019 (2019) 9017931.