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Targeting AMPK for the Alleviation of Pathological Pain

Marina N Asiedu, Gregory Dussor, and Theodore J Price

University of Texas at Dallas, School of Behavioral and Brain Sciences, JO 4.212, 800 W Campbell Road, Richardson, TX 75080, USA

Abstract

Chronic pain is a major clinical problem that is poorly treated with available therapeutics. Adenosine monophosphate-activated protein kinase (AMPK) has recently emerged as a novel target for the treatment of pain with the exciting potential for disease modification. AMPK activators inhibit signaling pathways that are known to promote changes in the function and phenotype of peripheral nociceptive neurons and promote chronic pain. AMPK activators also reduce the excitability of these cells suggesting that AMPK activators may be efficacious for the treatment of chronic pain disorders, like neuropathic pain, where changes in the excitability of nociceptors is thought to be an underlying cause. In agreement with this, AMPK activators have now been shown to alleviate pain in a broad variety of preclinical pain models indicating that this mechanism might be engaged for the treatment of many types of pain in the clinic. A key feature of the effect of AMPK activators in these models is that they can lead to a long-lasting reversal of pain hypersensitivity even long after treatment cessation, indicative of disease modification. Here, we review the evidence supporting AMPK as a novel pain target pointing out opportunities for further discovery that are likely to have an impact on drug discovery efforts centered around potent and specific allosteric activators of AMPK for chronic pain treatment.

Keywords

Neuropathic pain; Cancer pain; AMPK; mTOR; MAPK; Postsurgical pain

11.1 Introduction

Pain is the most common reason that people seek medical attention and is frequently a symptom of underlying injury or disease. Acute pain serves as a protective mechanism that alerts us to damaging or potentially damaging stimuli. Pain can, however, become maladaptive and persist for months or even years after an injury has resolved or emerge in the absence of any apparent injury (Woolf and Salter 2000; Basbaum et al. 2009). This sort of pathological pain is a major clinical and public health problem that adversely affects up to a third of the population of most developed countries and is associated with enormous medical costs and productivity loss in the workplace. (Education 2011). While acute pain can be well controlled with different treatments like nonsteroidal anti-inflammatory drugs or

theodore.price@utdallas.edu.

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opioids, very few effective therapeutics are currently available for pathological pain and most of them show limited efficacy (Education 2011). A possible reason for this lack of efficacy is that no therapeutics have yet been approved for human use that target underlying mechanisms that cause pain to become pathological. Rather, existing therapeutics (e.g., antiepileptics) only target mechanisms that transiently decrease pathological excitability in the peripheral or central nervous systems [PNS and CNS, respectively, (Baron et al. 2010)]. Hence, disease-modifying therapies to treat pathological pain are greatly needed to tackle the challenges posed by this medical problem.

In order to address how disease-modifying therapies for pathological pain can be developed, we must first elucidate the fundamental molecular events driving pathological pain development and maintenance. Work in this area using preclinical pain models has led to tremendous advancements, yet the molecular underpinnings of pathological pain are still not completely well understood (Mogil 2009). Nonetheless, it is well documented and broadly accepted that plasticity in PNS nociceptors, sensory neurons responsible for the detection of damaging or potentially damaging stimuli, and/or in CNS neurons that receive inputs from these cells promotes pathological pain (Woolf and Walters 1991; Perl 1996; Woolf and Salter 2000; Ji and Woolf 2001; Ji et al. 2003; Basbaum et al. 2009; Latremoliere and Woolf 2009; Price and Geranton 2009; Walters and Moroz 2009; Woolf 2011). This chapter will mainly focus on plasticity in peripheral nociceptors and how this form of plasticity can be targeted with adenosine monophosphate-activated protein kinase (AMPK)-based therapeutics (Price and Dussor 2013). We will showcase the evidence supporting AMPK activators as some of the first disease-modifying agents for pathological pain and highlight the rationale behind this premise as well as the relevant therapeutic strategies that can be utilized to engage AMPK in this therapeutic setting.

11.2 Activity-Dependent Translation as a Key Mechanism Promoting Pathological Pain and Its Negative Regulation by AMPK

Injury to peripheral tissues and/or peripheral nerves changes the sensitivity of nociceptive afferent neurons causing them to become hyperexcitable. The induction of this increase in excitability can occur rapidly after injury and is mediated by a variety of endogenous factors that act on diverse receptors expressed by nociceptors (Woolf and Walters 1991; Perl 1996; Koltzenburg 1999; Basbaum et al. 2009; Price and Geranton 2009; Reichling and Levine 2009; Walters and Moroz 2009). Very rapid changes in excitability are generally attributed to short-term signaling mediated by α subunits of G-protein coupled receptors (GPCRs) or via activation of kinases downstream of tyrosine kinase receptors (Trks) and can largely be attributed to the phosphorylation of ion channels. In some cases, these short-term changes in the sensitivity of nociceptors may resolve once the stimulus causing the signaling events to occur is removed. However, in cases where pain becomes pathological, this may not be the case. One possible explanation for how this occurs is that certain signaling events are capable of causing long-term changes in the function or phenotype of peripheral nociceptors causing potentially permanent alterations in pain sensitivity (Reichling and Levine 2009; Price and Inyang 2015). It is likely that this transition to a pathological pain state is controlled by changes in gene expression, either at the level of transcription (Woolf and

Costigan 1999; Ji and Woolf 2001; Obata and Noguchi 2004; Ji et al. 2007, 2009b) or translation changes (Price and Geranton 2009; Obara et al. 2012; Price and Dussor 2013).

Multiple lines of evidence indicate that a critical molecular event for neuronal plasticity is the activity-dependent regulation of translation, often at distinct sub-cellular locations, for instance at the base of dendritic spines or in axonal terminals (Martin et al. 2000; Giuditta et al. 2002; Klann et al. 2004; Sutton and Schuman 2005; Schuman et al. 2006; Jung et al. 2012). This process of activity-dependent translation has been linked to learning and memory in the central nervous system (CNS) and we will review evidence that it is linked to pathological pain in the peripheral nervous system (PNS). Local translation at distal sites (dendrites or axons) in neurons requires three features: 1) ribosomes must be present at distal sites, 2) mRNAs must be transported from the cell body to these distal sites, and 3) signaling machinery linking extracellular events to intracellular translation must be present and function downstream of cell surface receptors. In the CNS, these criteria are satisfied at the level of dendritic spines where molecular changes involved in learning and memory are thought to occur (Martin et al. 2000; Klann et al. 2004; Sutton and Schuman 2005; Schuman et al. 2006). In the PNS, including in nociceptors, there is now strong evidence that these criteria are also met (Jung et al. 2012), and there is also abundant evidence that local, activity-dependent translation plays a key function in changing the excitability of nociceptors (Price and Geranton 2009; Obara et al. 2012; Price and Dussor 2013).

An early view of translation of new proteins in the PNS was that this solely occurred in the soma of DRG or TG neurons (Koenig and Giuditta 1999). This idea was based on the limited number of ribosomes found in adult DRG axons. It is now well accepted that local translation in DRG neuron axons is an important component of development, especially at growth cones of developing DRG neurons. Following development, there are indications that local translation in axons is decreased; however, these axons still contain ribosomes, mRNAs, mRNA trafficking proteins, and signaling molecules involved in translation control (Koenig and Giuditta 1999; Mohr and Richter 2000; Piper and Holt 2004; Willis and Twiss 2006; Lin and Holt 2008; Jung and Holt 2011; Jung et al. 2012). Work in the area of pain plasticity has focused on signaling molecules with the major focus falling on a kinase called mechanistic target of rapamycin complex 1 (mTORC1). mTORC1 is regulated by upstream activation of Trks and engagement of PI3K/AKT signaling. When mTORC1 is activated, it stimulates phosphorylation of a family of proteins that bind to the 5' m7GTP Cap structure (5' Cap) of mRNAs (Gingras et al. 2004). A key event in this process is the phosphorylation of eukaryotic initiation factor (eIF) binding protein (BP) 4E-BP. When 4E-BP is phosphorylated by mTORC1, 4E-BP dissociates from eIF4E, the 5' cap binding protein, allowing for more efficient association of eIF4E with eIF4A (a deadbox family helicase) and eIF4G (a scaffolding protein) (Gingras et al. 2004). These three proteins form a functional unit called the eIF4F complex. This eIF4F complex is associated with efficient translation of target mRNAs and is an important regulatory endpoint for mTORC1 signaling (Gingras et al. 1999; Sonenberg 2008).

Augmented mTORC1 activity is unequivocally linked to plasticity in nociceptors. First, rapamycin, a highly selective inhibitor of mTORC1, attenuates plasticity induced by endogenous mediators that act via receptors expressed by nociceptive neurons (Price et al.

2007; Melemedjian et al. 2010). Rapamycin also decreases the sensitivity of a subset of nociceptors thought to play an important role in mechanical hypersensitivity following injury (Jimenez-Diaz et al. 2008; Geranton et al. 2009) and reduces neuropathic mechanical hypersensitivity in rats (Melemedjian et al. 2013c) and mice (Obara et al. 2011). Finally, factors that are well known to sensitize nociceptors, such as nerve growth factor (NGF), and peripheral nerve injury, which causes neuropathic pain, increase mTORC1 activity in DRG neurons and their peripherally projecting axons (Melemedjian et al. 2010, 2011). While much work has focused on mTORC1 in the PNS in pathological pain generation, there is also strong evidence linking increased mTORC1 activity to plasticity in the spinal dorsal horn after peripheral injury (Asante et al. 2009, 2010; Geranton et al. 2009; Norsted Gregory et al. 2010; Xu et al. 2010, 2011; Shih et al. 2012) or even exposure to drugs of abuse (Xu et al. 2014). Here, mTORC1 appears to control changes in synaptic strength between nociceptors and CNS neurons that relay nociceptive information to the brain via changes in postsynaptic expression of plasticity-related genes. However, an alternative interpretation is that presynaptic effects in the dorsal roots, which contain the central projections of DRG neurons, predominate, as there is also evidence that mTORC1 activity in these axons contributes to neuropathic pain (Geranton et al. 2009). While ongoing research is still elucidating the molecular details of how mTORC1 regulates nociceptor and dorsal horn neuron plasticity, it is clear that mTORC1 is a crucial molecular signaling hub underlying pathological pain.

MAPK represents another signaling pathway linking extracellular signals to translation in neurons, including nociceptors. The MAPK isoforms ERK and p38, which play crucial roles in nociceptor excitability and synaptic plasticity in the CNS, phosphorylate eIF4E at Ser 209 via a downstream kinase called MAP kinase interacting kinase [MNK, (Pyronnet et al. 1999)]. Two MNK isoforms are found in mammalian genomes and both are expressed in the nervous system. MNK-mediated phosphorylation of eIF4E is thought to regulate the translation of a subset of mRNAs. These mRNAs have been elucidated using mice where the Ser 209 site of eIF4E has been mutated to Ala rendering the protein unphosphorylatable (Furic et al. 2010). mRNAs whose translation is decreased in the absence of eIF4E phosphorylation encode cytokines, chemokines, and other plasticity-related proteins (Herdy et al. 2012). Among these mRNAs is the matrix metalloprotease isoform 9 (MMP9) (Gkogkas et al. 2014), which is expressed in the DRG, is regulated by injury and/or by chronic opioid exposure, and is involved in pathological pain (Kawasaki et al. 2008; Ji et al. 2009a; Berta et al. 2012; Liu et al. 2012). ERK or p38 signaling to eIF4E through MNK1/2 is also involved in the promotion of pain plasticity by endogenous factors that signal via this pathway through their cognate cell surface receptors. One such example is interleukin 6 (IL6). IL6 exposure to DRG neurons increases ERK and eIF4E phosphorylation and promotes mechanical hypersensitivity in a translation-dependent fashion (Melemedjian et al. 2010, 2013b, 2014; Asiedu et al. 2011).

The data discussed above point to mTORC1 and MAPK, especially ERK, signaling as prime targets for control of pathological pain. While a number of studies have indicated positive effects for the mTORC1 inhibitor rapamycin using an acute drug administration paradigm (Price et al. 2007; Jimenez-Diaz et al. 2008; Asante et al. 2009; Geranton et al. 2009; Melemedjian et al. 2010; Asiedu et al. 2011; Obara et al. 2011; Xu et al. 2014), longer term

treatment with rapamycin causes an engagement of feedback signaling through p70 S6 Kinase (p70S6K) in DRG neurons that leads to stimulation of ERK and augmented neuronal excitability (Melemedjian et al. 2013c). Human studies suggest that rapamycin treatment can promote pain hypersensitivity, and rapamycin treatment has been anecdotally linked to devastating human pain disorders such as complex regional pain syndrome (Christopher 2001; Witzig et al. 2005; Molina et al. 2008; Massard et al. 2010; Budde et al. 2011; McCormack et al. 2011). These rodent and human findings likely rule out rapamycin as a pain therapeutic. MAPK inhibitors have been widely investigated as pain therapeutics (Ji et al. 2009b) including some clinical trials for p38 inhibitors that have had mixed success (Anand et al. 2011). While work in that arena will undoubtedly continue, there is a strong scientific rationale for the development of therapeutics for pain that abrogate signaling in both the mTORC1 and MAPK signaling pathways as these are often convergently linked to nociceptor plasticity and pathological pain.

Emerging evidence indicates that AMPK activation negatively regulates activity-dependent protein synthesis and other signaling pathways that drive neuronal plasticity in pathological pain leading to decreased nociceptor excitability (Price and Dussor 2013). AMPK activation also suppresses the feedback signaling mechanism that arises from prolonged blockade of mTORC1 signaling with rapamycin (Melemedjian et al. 2013c). In addition, AMPK activation inhibits the MAPK signaling pathway through phosphorylation of adaptor proteins that regulate tyrosine receptor kinase signaling and through negative regulation of small GTPases that are upstream of MAPK signaling (Melemedjian et al. 2011; Carling et al. 2012; Tillu et al. 2012). Thus, mTORC1 and MAPK signaling pathways are both inhibited by AMPK activation suggesting that pharmacological stimulation of AMPK signaling may interfere with signaling that controls activity-dependent translation in nociceptors and therefore short circuit pain amplification. There is now strong evidence to support this novel role for AMPK as a pain plasticity target, which will be discussed in a variety of experimental contexts below.

11.3 AMPK as a Key Regulator of Ion Channel Activity and Its Role in Pathological Pain

The coupling of ion channel activity to the metabolic state of a cell is logical because ion flow across open cation or anion channels must be balanced by active transporters that consume a great deal of cellular energy. The activation of AMPK under cellular metabolic stress conditions and the well-recognized function of AMPK as a promoter of ATP generating catabolic pathways while turning off ATP-utilizing anabolic pathways (Hardie et al. 2012) posits that AMPK's modulation of ion channel function might result in decreased cellular excitability. Cystic fibrosis transmembrane conductance regulator (CFTR) was discovered by Hallows et al. as one of the earliest channel targets of AMPK. The direct phosphorylation of CFTR by AMPK inhibits the channel's activity by reducing its open probability (Hallows et al. 2000) and also preventing PKA stimulation of the channel (King et al. 2009).

AMPK was later reported to negatively regulate epithelial Na⁺ channel (ENaC) membrane expression in an indirect manner via phosphorylation of ubiquitin ligase Nedd4-2 which results in ubiquitination of ENaC and decreased ENaC expression (Carattino et al. 2005; Bhalla et al. 2006). While decreasing Na⁺ channel expression will result in decreased excitability, increased K⁺ channel activity will also decrease cellular excitability. In this regard, AMPK has been shown to enhance KATP (Kir6.2) channel activity and membrane expression (Sukhodub et al. 2007; Yoshida et al. 2012). Moreover, in outer hair cells of the ear, AMPK activation increases BK_{Ca} channel expression, which plays a role in protecting these cells from the excitotoxic effect of excessive sound exposure (Foller et al. 2012). On the other hand, AMPK has been shown to contribute to ion channel modulation that consequently increases cellular activity by driving hyperpolarizing shifts in the voltage dependence of Nav1.5 and decreasing current amplitudes of BK_{Ca}, TREK, and TASK channels (Light et al. 2003), as well as reducing the membrane expression of Kv7.1 and Kir2.1 channels (Andersen and Rasmussen 2012). Hence, there is evidence for bidirectional regulation of cellular excitability by AMPK activation. However, as we will argue below, the evidence gleaned from studies of AMPK in neurons overwhelmingly supports a role for AMPK in decreasing excitability in these specialized cells.

Activation of AMPK in rat hippocampal neurons produces a hyperpolarizing shift in the current/voltage relationship of voltage-gated K⁺ channels, an effect that was inhibited by introducing antibodies against Kv2.1 into the recording pipette. In addition, direct phosphorylation of Kv2.1 and shifts in channel kinetics similar to those observed in neurons were obtained in cell lines expressing Kv2.1 confirming AMPK's direct effect on regulation of Kv2.1 channels (Ikematsu et al. 2011). This study was among the first to show that AMPK activation results in enhanced K⁺ channel activity causing a robust decrease in neuronal excitability.

While further studies are needed to elucidate other ion channels that are directly targeted by the kinase, AMPK activation may also modulate channel activity or expression in neurons in an indirect manner similar to what was discussed above for ENaC. Nedd4-2, which is targeted by AMPK increasing its ubiquitin ligase activity, interacts with multiple channel types such as KCNQ channels, CIC-2 chloride channels, and voltage gated Na⁺ channels (Bongiorno et al. 2011). Thus, it is formally possible that AMPK-mediated Nedd4-2 activation may be a general channel modulatory mechanism resulting in channel downregulation in neurons, but this idea has not been rigorously assessed. AMPK-mediated interference with other kinase signaling pathways is another potential mechanism through which AMPK can decrease channel activity and therefore excitability in neurons. For instance, ERK has been shown to modulate numerous kinds of channels such as the K⁺ channel subtype Kv4.2 that contributes to transient outward or A-type K⁺ currents (Adams et al. 2000; Schrader et al. 2006), Cav2.2 channels (Martin et al. 2006), and Nav1.7 channels. The Nav1.7 channel is expressed prominently by nociceptors where it directs the amplification of generator potentials to control action potential firing (Stambouljian et al. 2010). Importantly, Nav1.7 is associated with human pain conditions wherein a loss-of-function produces congenital insensitivity to pain while a gain-in-function results in paroxysmal extreme pain disorder and erythromelalgia (Dib-Hajj et al. 2010). ERK phosphorylates Nav1.7 on specific residues on an intercellular loop of the channel. In

sensory neurons stimulated with depolarizing ramp current injection, ERK phosphorylation of Nav1.7 enhances action potential firing and decreases the latency to first action potential (Stambouljian et al. 2010). We have demonstrated that AMPK activators decrease ERK activity in nociceptors and dampen sensory neuron excitability evoked by ramp current injection (Melemedjian et al. 2011). Although a possible direct effect of AMPK on Nav1.7 cannot be completely excluded, the modulation of MAPK activity by AMPK likely orchestrates the observed reduction in neuronal excitability.

The evidence compiled above hints at two primary mechanisms through which AMPK can acutely influence the excitability of nociceptors: via direct phosphorylation events that likely increase the activity of voltage gated K^+ channels and through signaling mechanisms that dampen the activity of other kinases that phosphorylate channels involved in increased excitability. Additional studies are required to more fully grasp how these mechanisms operate in nociceptors. Nevertheless, the existing literature supports a role for AMPK activators for the treatment of pain because this mechanism is likely to both decrease activity-dependent expression of genes that promote excitability and to alter nociceptor excitability through decreased activity in excitatory channels and augmented activity in inhibitory channels. Next, we will discuss the accumulating preclinical evidence that supports AMPK activators as pathological pain therapeutics and their potential for disease modification in specific chronic pain states.

11.4 AMPK as a Target for Disease Modification in Neuropathic Pain

Neuropathic pain is defined as pain arising from injury or disease affecting the peripheral or central nervous system. Neuropathic pain influences a smaller proportion of the population than more common forms of persistent pain; however, it is among the most difficult forms of pathological pain to treat and places a significant burden on patients and healthcare workers. Because diseases that are rising in global prominence (e.g., diabetes) and treatments for other diseases (e.g., cancer chemotherapeutics) can cause peripheral neuropathies that result in unrelenting neuropathic pain, there is increasing emphasis on finding new therapeutic targets for neuropathic pain. Studies in rodents with traumatic injury to peripheral nerves highlight AMPK as a key and unique target for neuropathic pain alleviation (Melemedjian et al. 2011).

As noted above, injury to the PNS due to trauma, metabolic disease, or exposure to drugs, such as chemotherapeutics, is the fundamental etiology of neuropathic pain. The general symptomology of neuropathic pain includes exquisite hypersensitivity to mechanical stimulation, hypersensitivity to cold, and ongoing burning pain (Baron et al. 2010). Peripheral nerve injury (PNI) in rodents stimulates a reorganization of the translation machinery in the PNS characterized by an activation of mTORC1 (Abe et al. 2010; Melemedjian et al. 2011) and MAPK signaling (Obata et al. 2003, 2004a, 2004b; Agthong et al. 2006; Melemedjian et al. 2011) and their downstream signaling counterparts in DRG neurons and their axons. Additionally, there is an enhancement in the expression of RNA binding and transport proteins (Melemedjian et al. 2011) that is presumably involved in the translocation of mRNAs to the axonal compartment following injury (Zheng et al. 2001; Willis et al. 2005, 2011; Thakor et al. 2009; Ruangsri et al. 2011). In effect, these molecular

events induce an increase in the rate of translation in peripheral nerves (Melemedjian et al. 2011). Overall, this PNI-induced reorganization process may be linked to regeneration after injury (Willis and Twiss 2006; Jung et al. 2012) as well as changes in excitability observed in injured DRGs (Thakor et al. 2009; Melemedjian et al. 2011).

Systemic administration of AMPK activators (either metformin or A769662) to rodents after peripheral nerve injury decreases mechanical hypersensitivity, an effect that starts 2–3 days after treatment (Melemedjian et al. 2011, 2013c). Strikingly, within 7 days, these compounds produced a total resolution of mechanical hypersensitivity that still persisted following cessation of treatment, supporting the idea that AMPK activators have disease-modifying properties that develop over the course of treatment. Moreover, this disease-modifying effect of treatment with metformin does not seem to depend on when the treatment begins as 7 day systemic treatment reverses PNI-induced mechanical hypersensitivity when the onset of treatment was between 14 and 60 days after injury (Melemedjian et al. 2011, 2013c). In addition, the reversal of mechanical hypersensitivity after metformin treatment is sustained after a prolonged period of treatment cessation (Melemedjian et al. 2013c). Metformin treatment also normalized increased translation rates in injured peripheral nerves (Melemedjian et al. 2011), highlighting that the potential disease-modifying effects of AMPK activators on PNI-induced neuropathic pain are apparent from a behavioral and biochemical perspective. In vitro studies using patch-clamp electrophysiology on DRG neurons demonstrate that AMPK activators such as metformin and A769662 also reduce the excitability of these neurons (Melemedjian et al. 2011). Increased excitability of DRG neurons following injury is widely believed to result in ectopic activity causing ongoing burning pain that is a prominent feature of neuropathic pain (Baron et al. 2010). Although it remains to be shown in vivo, the profound effect of AMPK activators on DRG excitability suggests that AMPK activators might not only reverse mechanical hypersensitivity but also spontaneous pain associated with persistent neuropathic pain in humans.

An important mechanism of neuropathic pain is activation of glia in the spinal dorsal horn following peripheral nerve injury (Beggs and Salter 2010). This glial activation may lead to the secretion of inflammatory mediators such as cytokines and chemokines that act on neurons in the dorsal horn to enhance their excitability. Another apparent function of this change in glial activity is a decrease in their expression of glutamate transporters that leads to an enhancement of glutamatergic transmission between neurons in the dorsal horn (Nie and Weng 2009, 2010). Using a model of neuropathic pain in rats, Maixner et al. demonstrated that AMPK activation in the spinal cord leads to a reduction in glial secretion of cytokines (e.g., interleukin 1 β) and an increase in glutamate transporter expression that restores normal astrocyte-mediated control of synaptic glutamate levels in the dorsal horn after nerve injury (Maixner et al. 2015). A key finding of these studies is that these pharmacological effects are mimicked by genetic manipulation of spinal AMPK α 1 subunit expression. In another study, it was shown that blockade of AMPK activity in mice causes an enhancement of NLRP3 inflammasome activity and the generation of neuropathic pain-like behavioral effects (Bullon et al. 2015). This effect was absent in *Nlrp3*^{-/-} mice and could be rescued with subsequent treatment with metformin. Hence, AMPK activator-mediated control of neuropathic pain may have both peripheral and central components that

contribute to disease modification. More work is needed to delineate mechanisms underlying these effects.

11.5 A Triple Action for Ampk in Cancer Treatment, Chemotherapy-Induced Neuropathic Pain, and Cancer Pain

A core hallmark of cancer is the dysregulation of cellular energetics resulting in loss of normal regulation of cell growth and proliferation (Martinez-Outschoorn et al. 2010; Pavlides et al. 2010). The mTORC1 and MAPK have been widely implicated in cancer (Gao and Roux 2015; Siddiqui and Sonenberg 2015). A variety of cancer clinical trials have been conducted using mTORC1 or MAPK inhibitors. Clinical trials and preclinical investigations have shown that the use of single kinase inhibitors targeting these mechanisms can lead to the engagement of feedback signaling amplification in these kinase pathways that limits the utility of these therapeutics (Ghosh et al. 2006; Viciet et al. 2013) (Poulikakos and Solit 2011; Chapman 2013; Sale and Cook 2014). Using AMPK activators as a possible alternative approach to circumvent this problem is attractive from a molecular signaling standpoint because AMPK activation negatively influences both the mTORC1 and MAPK signaling pathways and attenuates feedback signaling mechanisms (Jakobsen et al. 2001). There is extensive literature highlighting the tumor suppressor function of AMPK activation. Oral administration of metformin in mice prevents tobacco carcinogen-induced lung tumorigenesis and significantly reduces the development of lung cancers (Memmott et al. 2010). In a model of chemically induced colon cancer, metformin markedly reduces aberrant crypt foci and decreases polyp formation (Hosono et al. 2010). Moreover, in widely cited metaanalyses of numerous diabetic epidemiological studies, there was evidence of a marked reduction in cancer risk and a significant improvement in prognosis in subjects taking metformin compared to those taking other antidiabetic drugs. These risk reductions were particularly associated with cancers of the colon, lung, and liver (Decensi et al. 2010; Hardie 2013). Hence, there is compelling evidence for cancer preventative and cancer therapeutic effects of AMPK activation.

Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting adverse effect of many chemotherapeutic agents (Balayssac et al. 2011; Ferrier et al. 2013) and can have devastating consequences for patients (Cata et al. 2006). Proposed therapeutics aimed at preventing the neurotoxic effects of chemotherapy have had limited success. Additionally, CIPN is resistant to many of the first-line treatments for neuropathic pain (Dworkin et al. 2010; Ferrier et al. 2013). Though the underlying mechanisms of CIPN are not well understood, some of the symptoms and pathophysiology such as epidermal nerve fiber dieback and ectopic activity in DRG neurons parallels that of trauma-induced neuropathic pain (Han and Smith 2013). Simultaneous administration of metformin with chemotherapy treatment in mice prevents the loss of tactile sensation and the development of mechanical hypersensitivity associated with chemotherapeutics (Mao-Ying et al. 2014). Notably, there is a lack of effect with metformin after the development of CIPN indicating that this therapeutic approach may only be effective when employed during the entire course of chemotherapeutic treatment (Mao-Ying et al. 2014). This is in stark contrast to trauma-induced neuropathic pain where metformin treatment resolved established

mechanical hypersensitivity. In spite of this, the active investigation of metformin as an add-on treatment for chemotherapy in cancer trials (Kourelis and Siegel 2012) suggests that this treatment approach may be valuable in the prevention of CIPN during the course of chemotherapy treatment and eliminate the dose-limiting side effect of chemotherapeutic agents.

CIPN is a major cause of pain in cancer patients; if certain cancers progress and metastasize to bone or originate in bone, these can cause severe pain. This cancer-induced pain can be caused by bone destruction induced by the proliferating cancer cells but there is also now strong evidence that the presence of cancer in bone causes alterations in the local microenvironment that alter the function and phenotype of nociceptors that innervate the bone. Many of these factors are cytokines, chemokines, and growth factors, like NGF, that act on sensory neurons to increase mTOR and MAPK signaling. In a rat bone cancer pain model, AICAR and resveratrol, two AMPK activators, cause a significant alleviation of cancer-induced pain that is accompanied by reduced cytokine expression and attenuation of MAPK signaling (Song et al. 2015). These authors also found a reversal of spinal astrocyte and microglial activation with resveratrol treatment suggesting that the CNS immune response induced by persistent nociceptor activation within the cancer-ridden bone is attenuated by AMPK activation (Song et al. 2015). Whether this is mediated by reduced nociceptor excitability in the PNS or a direct effect on CNS cell types remains to be thoroughly investigated.

While more work is clearly needed in this important area, these limited studies point to great opportunities for AMPK activators in the area of CIPN and cancer-induced pain therapeutics. The intense investigation of AMPK activators in cancer prevention and treatment makes it likely that clinical trials in this area will soon lead to opportunities to test these hypotheses in human beings. Investigators designing these trials should be cognizant of the fact that pain is a leading cause of disability and morbidity in cancer patients and survivors and design endpoints for pain measures into studies to examine the potential benefits of these compounds for cancer pain and CIPN in humans.

11.6 AMPK as a Target for Postsurgical Pain Treatment and Prevention

Pain is an unavoidable consequence of surgery. Despite the existence of analgesics aimed at managing acute postsurgical pain, chronic postsurgical pain still develops in up to 50% of surgical patients after certain surgical procedures, and it can be very debilitating in up to 10% of this population (Kehlet et al. 2006). Current therapies for postsurgical pain, which are mainly opioids, have serious side effects, abuse liabilities, and can eventually exacerbate chronic postsurgical pain or increase the chances of chronic postsurgical pain development (Laboureyras et al. 2009; Sehgal et al. 2013). The release of cytokines [e.g., IL6, (Clark et al. 2007; Loram et al. 2007)] and growth factors [e.g., NGF, (Zahn et al. 2004; Banik et al. 2005; Wu et al. 2007)] from the site of incision is one of the many causes of postsurgical pain and is likely linked to the development of chronic postsurgical pain. These endogenous factors, which can act via receptors expressed by nociceptors, perpetuate both phenotypic and functional changes in DRG neurons that result in increased excitability driving pain amplification and chronification (Banik and Brennan 2008; Xu and Brennan 2009).

Pain prior to surgery and/or a previous surgical procedure are the main identified risk factors for chronic postsurgical pain (Kehlet et al. 2006; Pinto et al. 2013). Studies have illustrated that there is an enhanced rate of chronic pain development after a revision to knee replacement surgery compared to an original knee replacement surgery. This points to the idea that the first surgery creates a pathological pain plasticity that alters the response to the second stimulus (the revision surgery) (Kim et al. 2014). The planned nature of surgical interventions presents a unique opportunity for the development of therapeutics targeting the prevention of chronic postsurgical pain development that can be utilized during a surgical procedure. Currently, there are no treatments available targeted at preventing the development of chronic pain after surgery.

The endogenous factors known to promote chronic pain after surgeries predominantly engage the mTORC1 and MAPK signaling pathways [e.g., NGF and IL6, (Zahn et al. 2004; Banik et al. 2005; Wu et al. 2007, 2009)] in nociceptors innervating the incision site to drive nociceptor sensitization pointing to AMPK activators again as a potential therapeutic approach to halt the development of incision-induced plasticity following surgery. Local application of resveratrol, which activates AMPK and decreases ERK and mTORC1 signaling in DRG neurons, at the time of incision in mice, or 24 h following incision, significantly attenuates incision-induced mechanical hypersensitivity (Tillu et al. 2012). Incision to the mouse paw induces a change in the nociceptive system such that a subsequent subthreshold stimulus administered after the incision causes a prolonged and enhanced mechanical hypersensitivity. This subthreshold stimulus shows no effect in naïve mice and is capable of evoking a pain state in “primed” mice even weeks after the incisional injury has healed. Hence, this form of plasticity may model the “second hit” scenario outlined above wherein the incidence of chronic postsurgical pain is very high (Kim et al. 2014). Notably, local resveratrol treatment at the time of the incision completely abolished the development of priming suggesting that AMPK activation may be used as a preventative treatment for chronic postsurgical pain (Tillu et al. 2012). Though this effect on chronic postsurgical pain is yet to be demonstrated with other AMPK activators, recent studies suggest that curcumin inhibits incision-induced pain and prevents incision-induced priming effects (Sahbaie et al. 2014). While the mechanism of action of curcumin was not explored in this study, curcumin activates AMPK in many cell types and likewise attenuates MAPK and mTORC1 signaling (Yu et al. 2008; Kim et al. 2009).

Collectively, these studies indicate that AMPK activation for the treatment of postsurgical pain achieves antinociceptive effects and prevents the development of persistent pain plasticity after incision. The work discussed above warrants further exploration with more specific AMPK activators in preclinical models but suggests that AMPK activators might be employed to reduce postsurgical pain and prevent the development of persistent pain after surgery.

11.7 AMPK Activators for Inflammatory Pain Treatment

The AMPK activators AICAR and metformin were recently evaluated in models of inflammatory nociception in mice (Russe et al. 2013) where both compounds attenuated inflammation-induced pain hypersensitivity and decreased the inflammatory response when

compounds were given systemically. AMPK activator treatment also reduced pain-associated activation of MAPKs in the spinal cord and the induction of c-fos expression in dorsal horn neurons. Importantly, in addition to a pharmacological approach, this study also evaluated the contribution of AMPK to inflammatory pain using mouse genetics. Using a global knockout approach for the AMPK $\alpha 2$ subunit, the authors found enhanced inflammatory hyperalgesia and a complete loss of the pain relieving effects of AMPK activators suggesting that the $\alpha 2$ subunit is the key regulatory factor for the antinociceptive effects of AMPK activators (Russe et al. 2013). In addition, these investigators also generated conditional knockout mice lacking the $\alpha 2$ subunit either specifically in sensory neurons or in macrophages and granulocytes. Both of these strains of mice showed enhanced inflammatory nociception suggesting that both sensory afferents and immune cells contribute to AMPK-mediated effects in the context of inflammatory pain.

An interesting new development in the area of therapeutics for inflammatory pain is the discovery that salicylates activate AMPK (Hawley et al. 2012) in addition to their very widely known action as irreversible cyclooxygenase (COX) enzyme inhibitors. The efficacy of salicylates in inflammatory pain has been widely attributed to this irreversible inhibition of COX, but it is formally possible that some of the beneficial actions are due to activation of AMPK with salicylates. Remarkably, other common nonsteroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and diclofenac also activate AMPK suggesting that an acidic structure found in many NSAIDs may also lead to AMPK activation albeit at higher concentrations than are needed to inhibit COX enzymes (King et al. 2015). COX-2-specific inhibitors apparently lack activity at AMPK (King et al. 2015). Given that COX-2-specific inhibitors have been disappointing as next generation inflammatory pain drugs, it is possible that they lose some degree of efficacy due to their inability to activate AMPK.

The discovery that the oldest anti-inflammatory pain medicines known to humans have activity at AMPK (Hawley et al. 2012; King et al. 2015) opens new opportunities for development of AMPK activating compounds for the treatment of inflammatory pain. A large number of COX inhibitors have been described [see, for instance, (Ramalho et al. 2009) for a recent review of compounds described in the patent literature], and screening efforts are underway to understand whether and how these compounds might interact with AMPK (Sisignano et al. 2016). Insofar as these COX inhibitors are clearly efficacious for inflammatory pain but have side effects that preclude their long-term use, these discoveries present great opportunity for rationale drug design for next generation inflammatory pain medicines with dual action at AMPK and COX and possible disease-modifying activities.

11.8 AMPK: Diabetic Neuropathy Prevention and Treatment

For several decades, metformin has been the first-line medication used for type II diabetes. Diabetes can cause irreversible damage to many organ systems when it is left unmanaged. Peripheral neuropathy is a common comorbidity of diabetes. The main symptoms of diabetic neuropathy are tingling and numbness in the distal extremities sometimes accompanied by burning pain (Argoff et al. 2006). Animal and human histochemical studies indicate that diabetes can cause dieback of PNS epidermal endings (Sorensen et al. 2006; Cheng et al. 2013; Cheung et al. 2015; Ebenezer and Polydefkis 2014), an outcome that may not be

related to pain (Sorensen et al. 2006). Also, in studies where diabetes is modeled in animals, the development of ectopic activity in DRG neurons (Khan et al. 2002; Serra et al. 2012) has been demonstrated. Clearly, diabetic neuropathy shares a similar pathophysiological profile with trauma-induced neuropathic pain and CIPN though its cause is mediated by metabolic dysfunction.

A current area of investigation is whether pharmacological treatments utilized in the control of glucose levels in type II diabetics are associated with protective effects against diabetic neuropathy. Though no conclusive studies in clinical populations have thus far been conducted, there are some indications that insulin treatment is associated with increased neuropathy incidence while metformin may protect against peripheral neuropathy. In a large study examining coronary artery disease and type II diabetes in a cohort of patients, the rate of neuropathy increased in patients using insulin whereas patients taking metformin had a reduced risk of developing neuropathy. This was independent of the duration of type II diabetes, glycemic index control, and other characteristics of the disease (Pop-Busui et al. 2009). These clinical results were further corroborated by a recent study in rats wherein a high fat diet (HFD) and streptozotocin (STZ) model of diabetes (HFD/STZ) was used to determine metformin's effect on the development of neuropathic pain. These authors found that metformin treatment started 4 days following the induction of diabetes had no effect on blood glucose levels over several weeks of treatment but significantly blocked the development of mechanical hypersensitivity caused by the HFD/STZ treatment (Byrne et al. 2015). This finding has now been corroborated by another study using a similar diabetes model in rats. These authors found that metformin treatment led to a significant reduction in diabetes-induced heat, cold, and mechanical hypersensitivity and reduced levels of glycation end products in blood in these animals without altering blood sugar levels (Ma et al. 2015). Importantly, this study also showed that metformin activates AMPK in sciatic nerves from diabetic rats and that this leads to the induction of AMPK-regulated genes in the PNS. The molecular mechanisms activated by metformin, and possibly other AMPK activators, that protect the peripheral nervous system during metabolic disease should be further explored. One possible mechanism for the neuroprotective effect of AMPK activation is via the induction of apolipoprotein E expression, a well-known neuroprotective factor, that is induced in the PNS by metformin treatment and is further enhanced by metformin treatment after nerve injury (Melemedjian et al. 2013a).

Additionally, AMPK may be directly and intimately linked to the development and maintenance of diabetic neuropathy. Hyperglycemia is a proposed contributing factor to nerve dysfunction in diabetes. It has been shown that hyperglycemia impairs bioenergetics in both DRG neurons and their mitochondria resulting in the downregulation of AMPK expression, phosphorylation, and activity (Roy Chowdhury et al. 2012). Elevating endogenous AMPK expression levels with adenoviral vectors or with augmenting AMPK activity using the AMPK positive modulator resveratrol restored the impaired biogenetic profile of cultured DRG neurons from streptozotocin-diabetic rats. In addition, resveratrol significantly reversed established deficits in thermal sensitivity and attenuated epidermal innervation density deficiency in STZ-treated rodents (Roy Chowdhury et al. 2012). These results suggest that deficits in AMPK may be a major driver of diabetic neuropathy

development. Taken together, the findings discussed here create a strong rationale for targeting AMPK as a promising therapeutic for diabetic neuropathy treatment.

11.9 AMPK and Morphine/Opioid Tolerance

Opioids such as morphine are the gold standard treatment for severe pain management (Manchikanti et al. 2011; Sehgal et al. 2013). Despite their efficacy in providing acute pain relief, persistent and long-term use of opioids produces a reduction in their analgesic efficacy, also known as tolerance, necessitating dose escalation to manage pain. This dose escalation heightens the risk for adverse side effects such as sedation, respiratory depression, and constipation associated with opioid use and drastically reduces the quality of life of patients (Xu et al. 2014). The mechanisms underlying opioid tolerance are complex and not well understood. Recent studies implicate opioid-induced microglia activation and the resulting pro-inflammatory cytokine production as key pathogenic players in opioid tolerance. Chronic morphine exposure activates spinal and cortical glial cells (Cui et al. 2008; Mika 2008) to induce microglia and astrocyte changes (Horvath et al. 2010) resulting in the enhanced secretion of many substances such as pro-inflammatory neuromodulators including interleukin-1 β (IL-1 β), IL-6, and tumor necrosis factor- α (TNF- α), CCL2, CXCL1, ATP, nitric oxide (NO) and excitatory amino acids which counteract the analgesic effects of morphine and accelerate the development of tolerance (Hameed et al. 2010; Zhao et al. 2012; Sun et al. 2014). Pharmacological inhibition of microglia reduces morphine-induced cytokine release and attenuates morphine tolerance (Mika 2008). Administration of microglial inhibitors, which suppress microglia activation and cytokine release, significantly attenuates the development of tolerance after chronic intrathecal or systemic opioid administration (Cui et al. 2008; Sun et al. 2012; Fukagawa et al. 2013).

The MAPK signaling pathway, including extracellular signal-regulated protein kinase (ERK), p38 MAPK, c-Jun N-terminal kinase, and extracellular signal-regulated protein kinase 5 (ERK5), has been implicated in morphine-induced neuroinflammation and tolerance (Chen and Sommer 2009). There is also indication that opioid-induced tolerance and neuropathic pain share some similar mechanism profiles (Watkins et al. 2005). Based on the evidence that AMPK activation inhibits MAPK signaling and that AMPK activators alleviate acute and neuropathic pain (Melemedjian et al. 2011; Tillu et al. 2012), Han et al. investigated the effect of AMPK activation on morphine-induced microglial activation and tolerance. They demonstrated that resveratrol, an AMPK activator, suppresses morphine-induced p38/NF- κ B signaling in microglia, and this effect was dependent on AMPK activation. They also showed that resveratrol blocks acute and chronic morphine tolerance (Han et al. 2014). This suggests that the engagement of AMPK signaling using AMPK activators represent a novel pharmacological method to attenuate morphine tolerance via suppression of morphine-induced microglial activation. Since opioids remain the most important drug class for the treatment of severe pain, this work creates a rationale for further exploration of AMPK activators as adjuvants to opioid therapy to reduce development of side effects that limit drug efficacy.

11.10 What Do We Know (and, More Importantly, Not Know) About AMPK Activators for Pain?

While there are a growing number of investigators actively working on AMPK as a novel target for pain therapeutics, we still have an enormous amount to learn about the target. In our view, the opportunity for disease modification via AMPK targeting presents the greatest opportunity for clinical benefit in patients suffering from chronic neuropathic pain. Neuropathic pain is perhaps the area of greatest unmet medical need in the clinical pain arena, and it is also heavily reliant on drugs that achieve little benefit in most patients (Baron et al. 2010). Having said this, it is still not known precisely how AMPK activators achieve this effect in rodent models of trauma-induced neuropathic pain, making it very difficult to make predictions of whether similar effects could be expected in human patients or even if trials should be designed with these endpoints in mind. Future work in this area should define the effects of AMPK activators on injured sensory afferents that drive persistent input to the CNS after nerve injury and on changes in microglia and other cell types in the CNS after injury (summarized in Fig. 11.1). While there is now substantial evidence that AMPK activation can influence both of these endpoints (Melemedjian et al. 2011, 2013c; Maixner et al. 2015), it is not clear which is responsible for the disease-modifying properties of AMPK activation in neuropathic pain. It is also, of course, possible that it is a different mechanism altogether (either AMPK-dependent or AMPK-independent) but investigations honing in on these two well prominent neuropathic pain mechanisms should yield preliminary insight into the problem.

Another major issue in the field is the reliance on imprecise pharmacological tools. This fact obscures whether AMPK is responsible for many of the behavioral observations that have been reported above. Before getting into how to combat this problem in future studies, two important points should be highlighted. First, metformin has been used widely in many of the preclinical studies described above. This is well justified because metformin is safe, widely available, and has the potential for immediate clinical translation. In fact, a retrospective study of metformin in low back pain patients suggests that the drug may be effective for sciatic nerve pain (Taylor et al. 2013), and a small prospective trial showed positive effects of metformin in fibromyalgia (Bullon et al. 2015). However, another retrospective study failed to find a positive effect for metformin on acute pain (Smith and Ang 2015). Metformin is widely thought to act via AMPK although this is still an area of great controversy and other mechanisms have been proposed (Zhou et al. 2001; Ouyang et al. 2011; Forslund et al. 2015). In agreement with this, a recent study investigating the effects of methylglyoxal, an important end glycation product produced in diabetes patients (Bierhaus et al. 2012), on diabetic neuropathic pain found that metformin blocked the effects of methylglyoxal via a direct reactive oxygen species sequestration mechanism that is independent of any intracellular signaling pathways (Huang et al. 2016). Second, while genetic tools have been employed in this area, their use is limited by the important function of AMPK in the development of the nervous system (Spasic et al. 2009). As noted above, genetic ablation of AMPK $\alpha 2$ subunits leads to an exacerbation of inflammatory pain and nullifies the antihyperalgesic effect of metformin (Russe et al. 2013). This finding strongly supports a mechanistic role for AMPK in modulation of inflammatory pain but similar

experimental strategies have not yet been undertaken in the setting of neuropathic or cancer pain models. Coming back to the issue of using imprecise pharmacological tools, two things can immediately be done in this area. First, investigators should look carefully at readily available data on the specificity of the AMPK blocker compound C and more carefully consider this in their interpretations. While compound C does inhibit AMPK kinase activity, it is one of the least specific kinase inhibitors available and should only be used under very specific experimental conditions where the use of the tool can lead to valid interpretations (Arrowsmith et al. 2015). Second, the past two or three years have seen a major proliferation in the availability of positive allosteric modulators of AMPK as well as an improvement in their potency and specificity (Giordanetto and Karis 2012; Tripodi et al. 2012; Xiao et al. 2013; Zhang et al. 2013; Liu et al. 2014; Dokla et al. 2015). While it is always possible that off target effects will be found for these compounds in the future, many of them possess different allosteric binding sites on AMPK and have distinct chemical structures. Carefully choosing pharmacological tools for activation of AMPK in experimental pain studies can lead to significant mechanistic insight and may open the door to new pharmacological strategies for AMPK activation in a broad number of chronic pain conditions. For instance, compounds that allosterically enhance AMPK activity via binding to the $\beta 1$ subunit [e.g., A760662, (Cool et al. 2006)] vs. those that protect against dephosphorylation via binding to the α subunit of the kinase [e.g., PT1, (Pang et al. 2008)] may have differential effects under different cellular circumstances but so far no work has been done on this area in the PNS or CNS. Findings along these lines would greatly enhance drug discovery efforts around AMPK as a pain target.

Work on AMPK as a pain target began based on mechanisms related to AMPK's role in regulating activity-dependent translation (Melemedjian et al. 2011; Price and Dussor 2013; Price et al. 2016) but it is still far from clear that this is the end of the story for AMPK-mediated control of nociceptor excitability, much less for other roles of AMPK activation in pain relief (e.g., modulation of microglial function). While it is clear that AMPK activation results in mTOR and MAPK inhibition in DRG neurons and a reduction in activity-dependent translation (Melemedjian et al. 2011; Price and Dussor 2013; Price et al. 2016), AMPK also regulates other cellular functions that may ultimately also be linked to inhibition of nociceptor excitability. For instance, AMPK is a core regulator of phospholipid biosynthesis and metabolism, but this aspect of AMPK function has been almost entirely ignored in the context of neuronal excitability. This area of investigation offers great opportunity for new discovery because it is well known that lipids are key regulators of channel, G-protein coupled receptor, and kinase function in nociceptors (Piomelli et al. 2014; Loo et al. 2015) and other neurons. Here, we propose that basic cell biology studies on the role of AMPK in neuronal excitability can greatly enhance our understanding of the target and how it can be manipulated to achieve effects that are relevant for pain therapeutics.

11.11 Closing Remarks

In this chapter, we have laid out the scientific rationale for targeting AMPK for the alleviation of pathological pain states and presented evidence in support of this therapeutic approach. While the existing evidence is compelling, we have tried to make the case that we

are only now scratching the surface of the potential for this novel target, and continued discovery in this arena of investigation is likely to lead to a clearer picture of how AMPK can best be targeted for the alleviation of different types of pain. What is already clear is that AMPK activators offer an opportunity for disease modification for some of the most challenging forms of chronic pain and that this target has the potential to lead to treatments that will greatly benefit patients who are terribly underserved by the available pharmacological armamentarium.

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Fig. 11.1.

Impact of AMPK activation on pathological pain-related signaling cascades. Factors associated with pathological pain employ signaling mechanisms that converge onto the mTORC1 and MAPK pathways to induce and maintain pain plasticity in nociceptors. Activation of AMPK abrogates these effects by negatively regulating these signaling events via phosphorylation of key effector molecules. AMPK activation phosphorylates IRS, an adaptor protein of the Trk receptor, at Ser789 to inhibit signaling via Trk and Insulin/IGF1 receptors. AMPK activation dampens mTORC1 signaling by phosphorylating TSC1/2 at Ser 1227 and 1345. The phosphorylation of Braf (Raf), a small GTPase linking receptors to MAPK signaling, by AMPK attenuates downstream ERK signaling. These signaling events produce several pathological pain attenuation outcomes such as: (1) a decrease in the phosphorylation of voltage-gated sodium channels such as Na_v1.7 leading to blunted neuronal excitability, (2) a reduction in microglial activation and microglia-related release of pro-inflammatory factors potentially resulting in reduced neuropathic pain, opioid-induced hypersensitivity, and diminished opioid tolerance, and (3) AMPK activation also normalizes dysregulation in mitochondrial and neuronal bioenergetics that is likely associated with diabetic neuropathic pain.