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Mini-review

AMPK: An emerging target for modification of injury-induced pain plasticity

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HIGHLIGHTS

- We review the form, function and pharmacology of AMPK.
- We review emerging evidence for a role of AMPK in neuronal plasticity and disease.
- We describe the potential role of AMPK in manipulation of pain plasticity.
- We describe novel opportunities to target AMPK for pain therapy.

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ABSTRACT

Chronic pain is a critical medical problem afflicting hundreds of millions of people worldwide with costly effects on society and health care systems. Novel therapeutic avenues for the treatment of pain are needed that are directly targeted to the molecular mechanisms that promote and maintain chronic pain states. Recent evidence suggests that peripheral pain plasticity is promoted and potentially maintained via changes in translation control that are mediated by mTORC1 and MAPK pathways. While these pathways can be targeted individually, stimulating the AMPK pathway with direct or indirect activators achieves inhibition of these pathways via engagement of a single kinase. Here we review the form, function and pharmacology of AMPK with special attention to its emerging role as a potential target for pain therapeutics. We present the existing evidence supporting a role of AMPK activation in alleviating symptoms of peripheral nerve injury- and incision-induced pain plasticity and the blockade of the development of chronic pain following surgery. We argue that these preclinical findings support a strong rationale for clinical trials of currently available AMPK activators and further development of novel pharmacological strategies for more potent and efficacious manipulation of AMPK in the clinical setting. Finally, we posit that AMPK represents a unique opportunity for drug development in the kinase area for pain because it is pharmacologically manipulated via activation rather than inhibition potentially offering a wider therapeutic window with interesting additional pharmacological opportunities. Altogether, the physiology, pharmacology and therapeutic opportunities surrounding AMPK make it an attractive target for novel intervention for chronic pain and its prevention.

Contents

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1. Introduction

The Institute of Medicine report on "Pain in America" published in 2011 highlights the urgent need for a better understanding of mechanisms that drive chronic pain and the development of therapeutics that target these mechanisms for the improved management of clinical pain disorders [1]. Pain is the most prominent reason that Americans seek medical attention and the lifetime population incidence of chronic pain in this country is 33%. This creates an enormous burden on medical care systems and society and leads to human suffering. An important goal of research in the pain area is to further understand mechanisms driving chronic pain and develop therapeutic strategies to treat pain based on these molecular insights. Herein we will focus on a novel target, AMP-activated protein kinase (AMPK), which directly targets signaling pathways that are involved in promoting chronic pain through the sensitization of peripheral nociceptors. This target is unique among kinases under investigation in the pain area because it can be pharmacologically targeted through an "agonist" based approach. The mechanism also provides a unique opportunity for immediate translation into the clinic because it can be engaged via activation by clinically available drugs, metformin and phenformin.

AMPK is a ubiquitous kinase endogenously activated by AMP and ADP and exogenously regulated by a variety of pharmacological entities including the widely prescribed anti-diabetes drug metformin [20]. AMPK is best known as a target for intervention in diabetes, largely due to the discovery that the kinase is a target, albeit indirectly, for metformin [92]. Work in the AMPK area has accelerated dramatically in the past decade and it is now clear that the kinase may play a central role in inflammation, cancer, neurological degenerative disorders and in the area of this review, pain. Accompanying advances in the basic understanding of AMPK function and its role in physiology have provided major inroads into pharmacological mechanisms for engaging AMPK activity [40]. While drug discovery around most kinases has focused on inhibition of kinase activity, largely through active site inhibitors, the role of AMPK as a negative regulator of other kinase pathways has long made it clear that pharmacological targeting of the kinase should involve activation, rather than inhibition [20,40]. This gives AMPK a somewhat unique position among kinases in the drug discovery area. The emergence of AMPK as a potential target for pain therapeutics is a relatively new development for the field, hence, our purposes for this review are to (1) introduce the form and function of the kinase, (2) to describe how the kinase can be targeted pharmacologically and then (3) to describe the work suggesting that targeting AMPK may lead to beneficial effects in the treatment of chronic pain.

2. Role of AMPK in cellular metabolism

Anabolic processes, such as protein synthesis, are orchestrated by upstream kinases that signal to the translation machinery [95] such as mammalian target of rapamycin complex 1 (mTORC1) and extracellular signal-regulated kinase (ERK) which signals via mitogen activated interacting kinases (MNK1 and MNK2) to the eukaryotic initiation factor (eIF) 4E. These kinases can be pharmacologically targeted individually by selective inhibitors or they can be negatively modulated by endogenous signaling factors that act on these pathways [113]. A crucial kinase for negative regulation of translation is the ubiquitous, energy-sensing kinase AMPK (Fig. 1, [20]). Activation of AMPK by depletion of cellular nutrients or through pharmacological intervention results in a dampening of signaling to the translation machinery [113]. This is the natural cellular response to energy deprivation wherein high AMP levels signal to AMPK thereby shutting down anabolic processes when nutrient levels are low [20]. AMPK is not solely regulated by cellular homeostatic mechanisms as it can also be targeted pharmacologically via a number of investigational compounds (e.g. AICAR and A769662 [24]), natural products (resveratrol [27,110]) and by the widely clinically available and safe drug metformin [79,92]. AMPK negatively regulates mTOR via activation of mTOR's negative regulator tuberous sclerosis complex 2 (TSC2) [25]. This results in a profound inhibition of mTOR and its downstream targets involved in translation control (e.g. eIF4E binding protein (4EBP) and ribosomal S6 kinase [25], Fig. 1). Activation of AMPK also negatively regulates ERK activity induced by growth factors and cytokines [54]. This likely occurs via phosphorylation of the insulin receptor substrate 1 (IRS1) protein at Ser 794 [101]. Because IRS-1 is a critical component of the signaling module of all tyrosine kinase receptors (Trks) [6], AMPK activation is likely to hinder Trk signaling (Fig. 1).

AMPK activation is not exclusively linked to negative regulation of protein synthesis. The kinase is also intimately associated with changes in glucose handling, fatty acid metabolism and plays an important role in the regulation of autophagy in cells. Hence, it is clear that AMPK plays a central role in regulation of diverse aspects of cellular metabolism. This central role likely emerges from AMPKs essential position as a cellular sensor of AMP and ADP. Because ATP is used as the proximal energy source in all cells, this mechanism is necessary to monitor cellular needs. Therefore, it appears that AMPK is essential for the monitoring of ATP levels and the diversion of cellular resources to the replenishment of ATP when cellular stores are depleted [20].

3. Physiological and pharmacological activation of AMPK in cells

To understand how AMPK is regulated it is necessary to understand the structure of the kinase. AMPK is made up of three subunits comprised of an α, β and γ subunit [20]. There are two isoforms of the α subunit, two isoforms of the β subunit and three γ subunit isoforms. The α subunit contains the serine/threonine kinase domain and the β and γ subunits are involved in regulation of the kinase containing subunit. Both the α and β subunits contain phosphorylation sites but the key site for upstream regulation appears to localize to the α subunit at threonine 172 which is phosphorylated by liver kinase B1 (LKB1). Phosphorylation of AMPK is a key regulator of kinase activity and the central endogenous regulator of AMPK, AMP, increases phosphorylation of the kinase. While the precise mechanisms through which this occurs are still not completely understood, it is clear that AMP binding to the γ