Role of mtor in pain

- Juliette Lanskey

Introduction

Pain perception protects the human body from damage, yet when the underlying mechanisms are disrupted pain can become a debilitating condition. There are almost 10 million Britains that suffer from pain on a daily basis affecting not only their personal wellbeing and quality of life but also the economy. Back pain is an example of chronic pain and back pain alone costs the NHS around £5billion per annum and it was reported that 4. 9 million days are lost per year to british businesses (http://www. britishpainsociety. org/media_faq. htm). Unfortunately, understanding the mechanisms that go awry leading to pain that is more harmful than beneficial is proving challenging. As a result, there is a deficit in treatments available to control chronic pain despite much research. There is therefore an urgent requirement to understand the mechanisms underlying pain perception in order for the development of therapeutics to reduce the sufferings of humans and the economy. This dissertation shall focus on a potential target, the mammalian target of rapamycin (mTOR), which recent research has highlighted as playing a significant role in chronic pain.

Pain Pathways

The processing of painful stimuli by the nervous system is termed nociception. Pain is nociception with additional psychological and emotional inputs. Noxious stimuli cause an action potential to run through a specialised set of neurons termed by Sherrington in 1906 as nociceptors; the pain neurons. Nociceptors have free nerve endings to detect noxious stimuli and can be classified into two main groups taking messages from the periphery

to the central nervous system, called Aï ¤ and C fibres. Aï ¤ fibres are medium-diameter, mylinated neurons and this myelination and wider diameter allows rapid signal conduction. It is the Aï ¤ fibres that transmit the first, sharp, localised pain of an injury whilst C fibres which are small-diameter, unmyelinated neurons transmit slow, diffuse, secondary pain 2009CELLULARANDMOLECULAR. Hence Aï ¤ fibres are crucial in rapidly signalling an injury whilst the slow, burning pain from C fibres is important for protection during the healing period.

These primary afferent nociceptors transfer messages from the periphery to the dorsal horn of the spinal chord. The dorsal horn is particularly important for processing and modulating noxious information. The dorsal horn is composed of six rexed laminae with transition zones approximately dividing different cell types. Indeed, nociceptors terminate in particular laminae. The majority of Aï ¤ fibres terminate densely in lamina I, though some do also terminate in lamina V. C fibres mainly terminate in laminae I and II, although there are also a few C fibre terminations in lamina V. Thus the majority of neurons which terminate in the superficial dorsal horn specifically respond to noxious stimuli while neurons terminating deeper in the dorsal horn tend to respond to innocurous touch (large diameter, rapid conducting Aï ¢ fibres transmit such innocuous information CELLULARANDMECHANMECHS2009).

It is within the dorsal horn that nociceptors synapse onto central projection neurons which transmit the noxious information up to the brain. The main central pathways run up to the brain via the thalamus or brainstem and terminate in areas such as the periaqueductal grey and the parabrachial nucleus REF. There are also descending pain pathways originating in the

periaqueductal grey, rostral ventral medulla and coeruleus which pass signals to the dorsal horn modulating nociception. There are also modulating circuits in the dorsal horn composing of exitatory and inhibitory interneurons contacting further neurons in the spinal cord (Fields2006thesis). Nociceptors have a pseudo-unipolar morphology allowing bidirectional signalling. This means that nociceptors are able to transmit action potentials antidromically from the the central nervous system to the nociceptor terminals (Dubin, 2010).

A result of central processing is increased sensitivity of the area at and around a site of tissue damage or inflammation (PUBHUNT). A chemical soup of cytokines and growth factors is released at the site of injury and causes an increase in the sensitivity of a subset of surrounding nociceptors. This means that these nociceptors have a reduced threshold for noxious stimuli (thus will now respond to less intense stimuli than before) and also an increased response to noxious stimuli. This sensitisation of neurons at the site of injury is called primary hyperalgesia. mTOR inhibitors do not affect primary hyperalgesia and thus it is unlikely mTOR is involved, however there is another phenomenon called secondary hyperalgesia which mTOR does seem to be involved in. Secondary hyperalgesia is when a set of neurons not directly at the site of injury but in the surrounding, undamaged area undergo an increase in sensitivity due to central processing (pubhunt). Recent studies have demonstrated that the mTOR plays a role in creating this sensitivity.

Acute pain is the pain that follows immediately after an injury to protect the body from further damage and aid the process of healing but when pain exists for more than 3 months it is defined as chronic pain

(SITETHESISMerskey and Bogduk, 1994; Russo and Brose, 1998). This chronic pain does not protect the body but rather hinders the quality of life. The pathology of chronic pain often consists of decreased pain thresholds and increased response to stimsuli; the nociceptors are more sensitive. Moreover, whilst nociceptors are generally silent, firing action potentials only when stimulated (dubin2010), in chronic pain, there is an increased tendency for spontaneous activity (JULIUSANDBASBAUMTHESIS). Altogether, chronic pain leads to allodynia (pain from a normally non-noxious stimulus), hyperalgesia (heightened sensitivity to noxious stimuli) and spontaneous pain.

mtor

The mammalian target of rapamycin is a regulator a number of cellular processes including synaptic plasticity, protein synthesis and cellular metabolism (XONCUETALTHESIS). It is a molecule belonging to the kinase family and forms two complexes with raptor; mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). It is when part of these complexes that it administrates its cellular functions though much more is known about mTORC1 and so it is predominantly the role of mTORC1 in pain perception that this dissertation shall focus on.

Signalling cascade

There is a signalling cascade involving mTOR, the downstream targets of which lead to cellular activities resulting in the organisation of the cytoskeleton, the regulation of metabolism and cell survival (wullschlegerTHESIS). The signalling cascade is initiated by a signal such as a neurotransmitter acting on transmembrane receptors which activate

phosphoinositol 3 kinase-AKT pathway. This results in the phosphorylation and thereby the activation of mTOR. Phosphorylated mTOR in turn phosphorylates the 4E-binding protein and in this phosphorylated state the 4E-binding protein is unable to bind and thus inhibit a protein called eIF4E. So when mTOR is activated it has the downstream affect of enabling eIF4E to associate with eIF4G, this is an essential step for initiating translation (TJ PRICE& GERANTON).

The fact that mTOR plays such a significant role in the regulation of translation is a hint of its importance in pain plasticity. Previously, it was thought by some that translation could only occur in the cell soma. However, others noted both the half-life of axonal proteins and the time it takes for a protein to travel down the length of the axon and concluded that the axoplasmic transport is too slow for protein synthesis only to occur in the cell soma HUNT. Indeed, following the discovery of ribosomes and ‘ Golgi outposts’ in dendritic spines it is now believed that local protein synthesis at the sites of dendritic synapses plays a significant role in plasticity (2009REVIEW).

Research demonstrates that chronic pain arises as a result of plastic changes that occur during persistent acute pain. During any pain there are noxious signals to the central nervous system enabling the pain to be perceived, if these signals persist it has been shown that this causes and maintains plastic changes that result in chronic pain. Indeed, it has been shown through advanced structural imaging methods that there are large scale alterations in the brain structure of sufferers of chronic pain CHRONICPAINPLASTICITY. There is relatively little research into the

possibilities of targeting this pain plasticity to help patients cope with chronic pain in comparison with genetic studies. It is consequentially an exciting new avenue of exploration and the role of mTOR in pain plasticity is of particular interest.

EARLIER – As mTOR plays such a crucial role in cellular function it is unsurprising that mTOR dysfunction is believe to be involved in a number of maladies. The role of mTOR in cancer, diabetes and neurodegeneration is being explored and a number of mTOR inhibitors have already been tested for treating certain maladies. For example….. This has demonstrated that mTOR inhibitors are potential treatment regimes BUT THERE ARE SIDEEFFECTS

MTOR – THESIS

MTOR SIGNALLING

MTOR & PLASTICITY – see 2009reviewnociception and AMPKPG 6 is v good

Dealing with pain MTOR AND RESEARCH – thesis

2Pain Pathways and Plasticity

3 The mammalian target of rapamycin *2007 – Decreased Nociceptive Sensitization in Mice Lacking the Fragile X Mental Retardation Protein: Role of mGluR1/5 and mTOR – mTOR's role in nociceptive synaptic plasticity through translation regulation; ' the mTOR inhibitor rapamycin inhibited formalin- and DHPG-induced nociception'*

…. mTOR is a major regulator of protein synthesis for it controls the initiation of translation (PUBLISHEDHUNT2009). It is thought that by controlling protein translation it maintains the sensitivity of nociceptors following local injury. Targetting mTOR could reduce the secondary hyperalgesia that occurs from pain and thus help patients cope with pain…

4 The mTOR signalling cascade

Unicellular organisms that are sensitive to nutrient availability in their environment control translation via a rapamycin-sensitive translation pathway. This process is controlled by a protein kinase, TOR, which is blocked by rapamycin. Interestingly, neurons appear to have co-opted this evolutionarily conserved mechanism to control activity-dependent local translation. Mammalian TOR, or mTOR, is activated by neurotransmitter receptor signaling cascades and phosphorylates downstream factors that control translation. Hence, mTOR is intricately involved in synaptic plasticity in the CNS, a mechanism that is linked to its role in controlling translation in dendrites (Jaworski *et al.* , 2006). The major mechanism of mTOR-regulated translation is control of the initiation of cap-dependent translation (depicted in Fig 1) (Gingras et al., 2004). This occurs because one of the major targets of mTOR phosphorylation is the elongation associated factor 4E-BP (Gingras *et al.* , 1999). 4E-BP binds c cap-binding factor eIF4E and, when it is hypo-phosphorylated, inhibits the formation of the eIF4E/eIF4G elongation complex preventing translation. When 4E-BP is hyper-phosphorylated, 4E-BP dissociates from eIF4E allowing eIF4G binding and the initiation of cap-dependent translation. Recently a small molecule inhibitor of eIF4G binding to eIF4E was discovered (4EGI-1) and this molecule inhibits cap-dependent

translation (Moerke et al., 2007). Hence, mTOR is crucial for regulating activity-dependent translation in neurons via its regulation of elongation factors (Banko *et al.* , 2006; Tang *et al.* , 2002; Tsokas *et al.* , 2007) and the mTOR pathway is amenable to specific pharmacological manipulation.

6Experiments suggesting inhibiting mTOR could help control pain

2007 – Decreased Nociceptive Sensitization in Mice Lacking the Fragile X Mental Retardation Protein: Role of mGluR1/5 and mTOR – mTOR's role in nociceptive synaptic plasticity through translation regulation; ' the mTOR inhibitor rapamycin inhibited formalin- and DHPG-induced nociception'

NOT THAT RELEVANT – basically saying that because of mutation translation can't happen properly…meaning mTOR has less control. However there is a subsection with rapamycin injections which does show decreased nociception with rapamycin

2011 – systemic inhibition of mTOR – mTOR regulation of nociceptive sensitivity; ' inhibiting the mTORC1 pathway systemically alleviated mechanical hypersensitivity in mouse models'

Good intro relating mTOR to chronic pain

Local cutaneous & intrathecal administration of rapamycin blocks activation of downstream targets of mTORC1 alleviating mechanical hypersensitivity – 21, 29 3 43 46 62 SHOULD PUT 1 OR 2 LOCAL EXPERIMENTS BEFORE THIS ONE

If targeting mTORC1 signaling pathway has a potential thera- peutic application for controlling chronic pain, systemic rather than local

administration (as has been used previously [21, 29]) requires further investigation. Here we examined the effective- ness of temsirolimus (CCI-779), a clinically used rapamycin ester derivative, given systemically