Institution: University College London / Birkbeck College

Unit of Assessment: 5 - Biological Sciences

Title of case study: Acid-sensing ion channels (ASICs), pain mechanisms and treatment

1. Summary of the impact

As a result of our discoveries of a new splice variant (ASIC1b) and a new member (ASIC4) of the ASIC family, and elucidation of their roles in pain caused by tissue acidity, several pharmaceutical companies are now working on ASIC-targeted analgesics and one company has been set up specifically to focus on this work. ASIC-related therapies for a wide variety of conditions are now in clinical trials, with substantial patient involvement. Our work has allowed new therapeutic applications to be conceived for already existing prescribed compounds, and for naturally-occurring compounds, that act on ASICs. Thus, our research on ASICs has had clinical and commercial impact.

2. Underpinning research

Unrelieved pain associated with ischaemia, arthritis, gastroesophageal reflux, tissue inflammation and injury is a major unmet medical need. In these conditions and many others, the associated pain often results from tissue acidosis, which activates proton-gated ion channels. Proton-gated channels expressed by sensory neurons are of particular interest as primary sensors generating pain. A major set of proton-gated channels in mammals are the acid-sensing ion channels (ASICs). Low extracellular pH can activate pain pathways by evoking an inward current through these channels, which are expressed in both the central nervous system and in peripheral sensory neurons. We cloned a variety of sensory neuron-specific proteins including some new ASIC channels **[1]**. These new ASIC channels provide a novel potential transduction pathway from low pH to the sensation of pain. We have discovered and delineated the involvement of two new ASIC isoforms – ASIC1b and ASIC4 – in the pain resulting from tissue acidosis.

In 1998, our lab cloned and characterised a new splice variant of acid-sensing ion channels named ASIC1b **[2]**. ASIC1b contains a unique N-terminal 172 amino acid region, as well as unique 5' and 3' untranslated sequences. ASIC1b, unlike ASIC1a, is found only in a subset of small and large diameter sensory neurons and is absent from sympathetic neurons or the central nervous system. Thus, the patterns of expression of ASIC1a and ASIC1b transcripts in rat dorsal root ganglion are distinct. When expressed in COS-7 cells, ASIC1b forms a functional channel with electrophysiological properties distinct from ASIC1a and ASIC3. The pH dependence and sensitivity to amiloride of ASIC1b is similar to that described for ASIC1a but, unlike ASIC1a, the channel is not permeable to calcium and ASIC1b-mediated currents are not inhibited by extracellular calcium. The unique distribution and properties of ASIC1b suggest that it may play a specialised role in sensory neuron function.

In 2000, we identified a further member of this ion channel family, ASIC4, which is developmentally regulated and expressed in a subset of sensory neurons, as well as in the CNS **[3]**. However, despite the strong homology with other ASICs, the ASIC4 transcript does not encode a proton-gated cation channel. Over the past several years, it has become apparent that ASICs, including ASIC4, are important regulators of pain pathways, either in primary transduction mechanisms or via other mechanisms **[4]**.

3. References to the research

[1] Akopian AN, Wood JN. Peripheral nervous system-specific genes identified by subtractive cDNA cloning. J Biol Chem. 1995 Sep 8;270(36):21264-70. http://www.ncbi.nlm.nih.gov/pubmed/7673161

[2] Chen CC, England S, Akopian AN, Wood JN. A sensory neuron-specific, proton-gated ion

channel. Proc Natl Acad Sci USA. 1998 Aug;95(17):10240-5. http://dx.doi.org/10.1073/pnas.95.17.10240

[3] Akopian AN, Chen CC, Ding Y, Cesare P, Wood JN. A new member of the acid-sensing ion channel family. Neuroreport. 2000 Jul;11(10):2217-22. http://www.ncbi.nlm.nih.gov/pubmed/10923674

[4] Donier E, Rugiero F, Jacob C, Wood JN. Regulation of ASIC activity by ASIC4 - new insights into ASIC channel function revealed by a yeast two-hybrid assay. Eur J Neurosci. 2008 Jul;28(1):74-86. http://dx.doi.org/10.1111/j.1460-9568.2008.06282.x

Example of a major grant: Wellcome Trust. Regulation of peripheral pain thresholds. 04/2002-03/2005. 065593/Z/01/Z. £401,899

4. Details of the impact

i. New clinical studies with patient involvement

By highlighting the importance of ASICs in pain regulation, we have increased the potential targets for research in patient populations across a range of conditions, and this is reflected by the recent increase in clinical studies focused on these channels. In the last three years, six clinical studies have been initiated to look at the involvement of ASICs in – and the effects of ASIC-targeted drugs on – conditions such as inflammatory pain, optic neuritis, and gastroesophageal reflux. These studies involve over 400 participants, including patients and healthy volunteers **[a]**.

ii. Novel drug and treatment development for pain and disease

The world market for pain management drugs and devices reached $34.9 billion in 2012, growing at a rate of 2.9% from 2010 to 2012. The market is growing as a result of the aging population, but also because of increased awareness of pain and the need for treatment, among other factors **[b, c]**. The major challenge in the pain drug market is to reduce the side-effects associated with treatment, and our discovery of roles for ASIC1b and ASIC4 in the pain caused by tissue acidosis – which accompanies a variety of conditions from arthritis to gastroesophageal reflux – has provided the pharmaceutical industry with ideal targets for the development of more specific analgesics which will have widespread applications.

Our discovery that ASIC1b is only expressed in the peripheral nervous system, and has a sensory neuron-specific distribution and more selective ion permeability than other members of the ASIC family, makes it arguably the most promising of the ASIC targets for drug development. Indeed, more than 40 patents on treatments and compounds targeting ASIC1b are now held worldwide **[d]**. As well as analgesic compounds, these patents also cover ASIC-focused treatments of conditions such as ischaemic brain injury **[e-1, e-2]**, epilepsy **[e-3]**, and demyelinating diseases such as multiple sclerosis **[e-4]**.

iii. New ASIC-focused pharmaceutical company created

Our research has shown that ASICs are important regulators of pain pathways, and these channels are thus valuable therapeutic targets. In 2008, Sophia Antipolis established Theralpha, a dedicated ASIC-focused pharmaceutical company derived from the pioneering studies of Michel Lazdunski in France and the Wood group at UCL, focused on the development and commercialisation of innovative therapies for the treatment of pain. They are "advancing next generation pain drugs based on scientifically validated Acid Sensing Ion Channel (ASIC) pathways", and so far have developed compounds targeting ASIC1a, ASIC3 and ASIC1b (one of the channels we cloned). They describe their programme as follows **[f]**:

> "*There has been a lack of clinical breakthroughs in recent years, and current therapies are often inadequate, have side effects, or are under-prescribed due to the dangers of*

addiction.

Theralpha aims to develop its pipeline to address unmet medical need in pain, a significant economic burden where more than 300 million people worldwide suffer. The chronic pain market is currently valued at $30 billion and is forecast to reach more than $47 billion by 2023.

Our lead product, THA903 is designed to address acute pain by sublingual administration. We have three additional product candidates in preclinical development [THA901, for the treatment of neuropathic and postoperative pain; THA902, for the treatment of inflammatory pain; and THA904, a natural peptide in drug discovery" which acts on the ASIC1b-containing channels that the Wood group at UCL discovered **[g]**.

By informing the development of novel pain-relieving compounds by a pharmaceutical company that specialises in ASIC-based therapies, our research has had commercial and economic impact on the pain drug market.

iv. Sites of action of existing therapeutic and naturally-occurring compounds uncovered

Our identification of a novel ASIC splice variant and a new member of the ASIC family has allowed mechanisms of action of existing compounds to be uncovered, thus increasing the clinical understanding and potential therapeutic application of commonly prescribed drugs (such as amiloride), and highlighting a therapeutic role for naturally-occurring analgesics (such as peptides in black mamba venom).

Amiloride is a potassium-conserving diuretic, usually prescribed to treat water retention and hypertension. ASICs are sensitive to amiloride, and our lab showed that amiloride inhibits the current through ASIC1a and ASIC1b to a similar extent (see Underpinning Research section). In the light of amiloride's antagonistic effect on ASIC channels, this drug is increasingly being considered as an ASIC-based analgesic as well as a diuretic, and four clinical studies are now testing amiloride for the treatment of painful conditions such as pressure ulcers, heartburn, optic neuritis and human inflammatory pain **[h]**.

Recently, a new class of three-finger peptides from black mamba venom has been shown to abolish pain through inhibition of ASICs expressed either in central or peripheral neurons, including inhibition of peripheral ASICs containing the ASIC1b subunit that we cloned **[g]**. These peptides, termed mambalgins, are not toxic in mice but show a potent analgesic effect upon central and peripheral injection that can be as strong as morphine. Inhibition of ASIC1a and ASIC2a subunits in central neurons and of ASIC1b-containing channels in nociceptors is thought to be involved in the analgesic effect of mambalgins. Thus our cloning of ASIC1b has led to the identification of a mechanism (a key step for regulatory approval) by which natural peptides that block this target can produce a potent analgesia.

5. Sources to corroborate the impact

[a] New clinical studies on ASICs involving patient groups and healthy participants: six new studies are revealed when the USA clinical trials database, ClinicalTrials.gov, is searched for the term "ASIC". http://clinicaltrials.gov/ct2/results?term=asic&Search=Search

[b] *Treating Pain a 35 Billion Dollar Business for Pain Management Drug and Device Market: New Kalorama Information Report* – New York, NY (PRWEB) June 03, 2013. http://www.prweb.com/releases/2013/6/prweb10794431.htm

[c] *The World Market for Pain Management Drugs and Devices* – May 20, 2013, Pub ID: KLI5042319: http://www.kaloramainformation.com/Pain-Management-Drugs-7579512

[d] **Number of patents for compounds targeting sodium channels:** Wipo patent database

search for “ASIC1b” in Any Field reveal 43 hits.

[e] **Example non-analgesic WIPO patents returned when searching for “ASIC1b”:**

1. US20120087865: Treatment of ischaemia
2. US20080279965: Treatment of injury to the brain by inhibition of acid sensing ion channels
3. US20080242588: System for seizure suppression
4. US20100015127: Treatment for demyelinating disease

[f] Theralpha: an ASIC-focused pharmaceutical company developing new therapies for the treatment of pain including blockers of ASIC1b (the channel we cloned) in the PNS. http://www.theralpha.com/

[g] Diochot S, Baron A, Salinas M, Douguet D, Scarzello S, Dabert-Gay AS, Debayle D, Friend V, Alloui A, Lazdunski M, Lingueglia E. (2012) Black mamba venom peptides target acid-sensing ion channels to abolish pain. Nature. 490(7421):552-5. **[shows mamba toxin blocks ASIC1b in the peripheral nervous system]**. http://www.nature.com/nature/journal/v490/n7421/full/nature11494.html

[h] New clinical studies on amiloride’s action on ASICs: Four new studies revealed when the USA clinical trials database, ClinicalTrials.gov, is searched for the terms “amiloride” and “ASIC”. http://clinicaltrials.gov/ct2/results?term=amiloride+asic&Search=Search