Available online at www.sciencedirect.com

SciVerse ScienceDirect

Current Opinion in Pharmacology

Understanding anomalous adaptation in chronic pain for successful development of disease modifying drugs

Editorial overview

Giacinto Bagetta and Shinobu Sakurada

Current Opinion in Pharmacology 2012, **12**:1–3

Available online 13th December 2011

1471-4892/$ – see front matter

DOI 10.1016/j.coph.2011.11.002

Giacinto Bagetta

Department of Pharmacobiology and University Consortium for Adaptive Disorders and Head Pain, Section of Neuropharmacology of Normal and Pathological Neuronal Plasticity, University of Calabria, 87036 Rende (Cosenza), Italy
e-mail: g_bagetta@virgilio.it

Giacinto Bagetta graduated in medicine in 1983 and consultant in pharmacology since 1987, has been appointed in 1994 full professor of pharmacology at the School of Medicine of the University of Cagliari. Since 1995 he is Chairman of Pharmacology at the University of Calabria and, since 1998, Founder and Coordinator of the PhD School of Pharmacology and Biochemistry of Cell Death. Since 2006 he is Head of the Centre of Neuropharmacology of Normal and Pathological Synaptic Plasticity in the frame of the University Consortium for Adaptive Disorders and Head Pain established in Pavia. His main research interests encompass basic and translational aspects of cell death occurring in acute (brain ischemia) and chronic (glaucoma) neurodegenerative diseases and neuropathic pain. Author of 137 articles in indexed journals, he co-edited seven books published by Elsevier plc, CRC Press and Portland Press (see http://gbagetta.jimdo.com).

Member of Italian and International Societies of Pharmacology and Neuroscience, before being associated to the *Current Opinion in Pharmacology* he served as member of the Editorial Board of *Journal of Neurochemistry*, *Neuroscience Methods* and *Journal of Chemotherapy*, among others. Since 2004 he has been member of the National Health Research Committee at the Italian Ministry of Health.

Shinobu Sakurada

Department of Physiology and Anatomy, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan
e-mail: s-sakura@tohoku-pharm.ac.jp

Shinobu Sakurada graduated in pharmacy in 1969 and got PhD degree in 1978, Shinobu Sakurada has been appointed in 1996 as a Chairman and professor of physiology and anatomy at the Tohoku Pharmaceutical University. He is member of the Executive Committee of Tohoku Pharmaceutical University since 2004, and Board of the directors of Tohoku Pharmaceutical University since 2007. His main research interest encompasses the mechanism of neuropathic pain (nerve injured neuropathy, inflammatory chronic pain, cancer pain, multiple sclerosis), and development of new opioid receptor agonists as analgesics. He is the author of 274 full papers in internationally indexed journals and co-editor of two books.

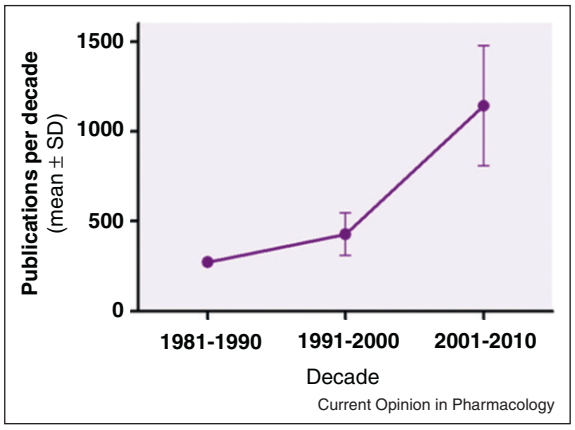
He is member of Japanese and International Narcotics Research Conference, International Association for the study of Pain, Japanese Society for Pharmaceutical Palliative Care and Sciences, Japanese Pharmacological Society, Japanese Society of Neuropsychopharmacology, Japanese Society of Pharmacy, and Physiological Society of Japan. He has served as member of the Editorial Board of Peptides.

Pain is among the most dynamic areas of neuroscience research. This is at least partly documented by the impressive and steady increase in indexed publications over the past decade (Figure 1). This growing interest is mainly due to the major advances brought to basic research and human studies by modern molecular, genetic, electrophysiological and imaging techniques, together with the impelling need of National Health Systems to deal with this costly, but still poorly managed, pathological condition.

Examples of how advanced methodologies can provide new insights in to the mechanisms of nociception and pain come from the review by Prof J.N. Wood and Dr N. Eijkelkamp. In fact, the combination of neuronal silencing strategies, cell depletion and gene deletion has provided us with new insights into the particular cell types that discriminate between different mechanical stimuli and indicated TRPA1 channel as potential mammalian mechanosensor (i.e. mechanically gated ion channel). However, the expression of such an activity has not yet been demonstrated using heterologous expression. The effort in searching for a mammalian neuronal homologue mechanotransducer (i.e. epithelial Na channel, ENaC) described in *C. elegans* has yet generated disappointing results. Another member of the superfamily of TRP channels, TRPV1, a ligand-gated cation channel, has generated excitement as potential therapeutic target. Prof S. Maione and colleagues report on our actual understanding of this polymodal nocitransducer widely expressed within pain transmitting, modulating areas of the peripheral and central nervous system.

The extensive plasticity shown in normal and pathological disease states by peripheral and central neural relays mediating nociception is stressed by Prof J. Sandkühler and Dr D. Gruber-Schoffnegger. In particular, in nociceptive pathways long-term potentiation (LTP), the electrophysiological correlate of learning and memory, shares principle features with hyperalgesia including induction protocols, pharmacological profile, neuronal and glial cell types involved and means for prevention. Calcium signaling (i.e. PKC, ERK or CREB), triggered downstream ionotropic and metabotropic glutamate (Glu) receptor activation, is implicated in most of activity-dependent forms of LTP at C-fiber while ATP and BDNF is dependent on p38MAPK. LTP at synapses between nociceptive nerve fibers and principal pain neurons causes hyperalgesia. Reversal of LTP, that is, 'depotentiation' thus constitutes potential means to erase memory traces of pain. Interestingly, while ionotropic Glu receptors are not considered good target for pain treatment, inhibition of group I mGlu receptor-mediated signaling and potentiation of group II and III mGlu receptor signaling are effective strategies to achieve analgesia (Dr S. Chiechio and Prof F. Nicoletti).

Figure 1



The graph illustrates the number of publications on neuropathic pain appeared in medline between 1981 and 2010 and distributed per each given decade.

It is well established that crucial mechanisms to memory formation include epigenetic changes, that is, chemical modifications to chromatin which modulate gene activity without altering the DNA sequence. The view of Dr S.M. Géranton is that the latter require similar synaptic plasticity to pain processing, indicating that they may play a key role in the control of pain states. Incidentally, an epigenetic approach leading to an increased expression of mGlu2 receptors has been proven to have good effects in different pain models. In addition, it is predicted by Dr S.M. Géranton that drugs used clinically to target the epigenetic machinery for the treatment of cancer might also be useful for the management of chronic pain.

Downstream to the control of gene transcription, the importance of local translation of mRNA as regulator of nociceptor sensitivity is highlighted by Prof S.P. Hunt and his colleagues. Thus, the sensitivity of a subset of fast-conducting primary afferent nociceptors is thought to be regulated by the complex 1 of mTOR (mTORC1) signaling pathway. In fact, activated mTOR is expressed largely in myelinated sensory fibers in mouse and inhibiting the mTORC1 pathway systemically alleviates mechanical hypersensitivity in mouse models of inflammatory and neuropathic pain [1].

A defect in one or more of the basic homeostatic pathways regulating neuronal health may result in progressive neuronal dysfunction. As highlighted by Dr L. Berliocchi and colleagues, this does not necessarily implicate neuronal death, but it may lead to maladaptive changes in neuronal signals. Thus, in the spinal cord, disruption of the autophagosome/lysosome system may contribute to the pathogenesis of neuropathic pain [2].

More established, though not completely dissected, is the role in peripheral and central sensitization of the complex network of pro-inflammatory cytokines and chemokines. While Dr N. Kiguchi and colleagues refer in particular to the chemokine CCL2 and the adipokine leptin, Dr R. Lattanzi and Prof L. Negri focus on the role of the pro-inflammatory and drugable Bv8/prokinetins system and their receptors in peripheral and central sensitization. Among other chemokines, Dr E.A. Old and Dr M. Malcangio discuss the involvement of the CX3CL1/CX3CR1 pathway in the hypersensitivity and spontaneous firing that is characteristic of central sensitization and that provides a feedback mechanism to further activate microglia. Neuronal CX3CL1 is liberated by CatS, a lysosomal protease released by microglia following activation of the P2X7 receptor by high concentrations of ATP likely to be neuronal in origin, highlighting the importance of the cross-talk between these two cell types.

P2X receptors (P2XRs), together with P2Y receptors (P2YRs), are also promising targets for treating neuropathic pain as reviewed by Prof K. Inoue and colleagues. One expected advantage of interfering with microglial P2XRs and P2YRs is that normal pain sensitivity would be unaffected since most of these molecules are upregulated, or their activities enhanced, mainly in activated microglia present in areas of the spinal cord where damaged sensory fibers project. Purinergic agents, including P2X3 and P2X2/3 receptor antagonists that are orally bioavailable and stable *in vivo*, as well as agents modulating ATP release and breakdown are introduced by Prof G. Burnstock as therapeutic strategies ready for translation into clinic for the treatment of visceral pain in conditions such as renal colic, interstitial cystitis and inflammatory bowel disease.

Actually, some of the most powerful painkillers belong to the opioid family of analgesics though these are low efficacy therapeutics for treating neuropathic pain and, unfortunately, prolonged exposure to these analgesics can cause severe adverse side effects, including physical and psychological addiction. However, there is a continued effort to identify painkillers whose underlying spectrum of actions differs from opioids principally for safety characteristics. To this aim, Dr H. Mizoguchi and his colleagues synthesized, among others, compounds like amidino-TAPA and described their analgesic profile, very probably mediated via the release of endogenous κ-opioid peptides thus being devoid of addictive effects and more efficacious on neuropathic pain.

The introduction at the turn of the twenty-first century of mRNA microarrays and subsequent mRNA seq has led to whole genome expression profiling that, in conjunction with clinical genetics, dramatically improved our understanding of the molecular phenotype of a cell/diseased body by comprehensively quantifying mRNA content

[see [3]]. Using these technologies, Prof C. Woolf and his colleagues have identified three enzymes, that is, GCH1, SPR and QDPR, critical to the control of intracellular levels of tetrahydrobiopterin (BH4) in injured sensory neurons. This discovery allowed their relevance to the initiation or persistence of chronic pain to be proven and, quite importantly, to repurpose sulfasalazine, an old drug approved for inflammatory bowel disease therapy, for chronic pain treatment on a rational basis.

Excitement has been recently generated by the positive results of clinical trials showing that local injections of BOTOX® (BoNT/A complex) reduce chronic migraine symptoms including frequency and intensity. More importantly, Prof J.O. Dolly and Dr M.A. O'Connell report that this strategy, reliant on proteolytically inactivating intra-neuronal SNARE proteins which are essential for regulated exocytosis of transmitters and peptides and other pain signaling molecules, is amenable to further protein ingenerization to yield longer lasting and more effective pain remedy.

To conclude, new roads of highly competitive research have been opened during the most recent years. These will drive us to the successful targeting of the dysfunctional neuron with next generation disease modifying drugs with which to control chronic pain.

We would like to acknowledge the effort of all the contributors to this Neurosciences issue on Pain and a special thank goes to the staff of the Editorial office of Current Opinion in Pharmacology. In particular, we would like to acknowledge the professional and skillful collaboration of Mrs Pien Van Spijker and Mrs Hanna Van de Watering. Finally, we both remain indebted with the Referees that have contributed to our editorial work.

References

1. Obara I, Tochiki KK, Géranton SM, Carr FB, Lumb BM, Liu Q, Hunt SP: **Systemic inhibition of the mammalian target of rapamycin (mTOR) pathway reduces neuropathic pain in mice**. *Pain* 2011, **152**:2582-2595.

2. Berliocchi L, Russo R, Maiarù M, Levato A, Bagetta G, Corasaniti MT: **Autophagy impairment in a mouse model of neuropathic pain**. *Molecular Pain* 2011, **7**:83 doi: 10.1186/1744-8069-7-83.

3. Neely GG, Hess A, Costigan M, Keene AC, Goulas S, Langeslag M, Griffin RS, Belfer I, Dai F, Smith SB *et al.*: **A genome-wide Drosophila screen for heat nociception identifies α2δ3 as an evolutionarily conserved pain gene**. *Cell* 2010, **43**:628-638.