Pain research: what have we learned and where are we going

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We have always wondered why do we feel pain, how is it caused, what it means to us and, more importantly, how can we prevent or reduce it. We can trace the origin of pain research back to the beginning of our time on earth. From spiritual...
beliefs of supernatural punishment for our sins to scientific theories of brain function, mankind has always regarded pain as one of the fundamental aspects of our life, a powerful drive of our emotions and an effective learning tool. As Aristotle put it ‘we measure our actions by the rule of pleasure and pain. For this reason, then, our whole inquiry must be about these’. Notwithstanding this long tradition of enquiry into pain and pain mechanisms, we have witnessed in the last decades a profound transformation in the social perception and appreciation of pain, which in turn has influenced the scientific and medical approach to pain research and management. Let us look at this social transformation, how it has driven our enquiry into pain mechanisms and how our new knowledge translates into ways to reduce or eliminate pain. And let us also reflect on the future of pain research.

**Pain and society**

Browse through any recently published book or current review on pain mechanisms and management and you will soon find statements to the fact that pain is not a symptom but a disease in its own right. This represents a major change in the social perception of pain, a departure from centuries of considering pain an inevitable symptom of disease that should be borne with courage and fortitude, a test of our character and a measure of our resilience. Today society demands a pain free world, no more painful births, no more painful surgeries, no need to add pain to the burden of disease and, when the time comes, no more painful agonies; we want a painless exit from life. Patients are told not to suffer in silence, to insist on more effective analgesia and to regard pain as a nuisance that should be eliminated. Medical organizations and prominent individuals are actively campaigning to include pain treatment as one of the fundamental human rights and are running initiatives to address the societal impact of pain and to persuade governments to dedicate funds and resources to treat pain as a disease in its own right. Some of these initiatives are influenced and driven by the pharmaceutical industry, which is likely to benefit from an increased availability and prescription of analgesics, but none of them would be successful if they were lacking a strong social support. The social impetus is the original and main drive and the medical organizations and the pharmaceutical industry are steering the process and giving a professional platform to the movement.

The main consequence of this social transformation has been a considerable increase in research into pain mechanisms, particularly those aspects of pain related to clinically relevant conditions. Also, pain medicine has emerged as a distinct medical specialty with its own areas of intervention. Multidisciplinary pain clinics are now commonplace in hospitals and health centres, run by professionals who deal exclusively with pain not only as a symptom but also as a disease. Organizations such as the International Association for the Study of Pain and its many national chapters have pioneered and led other similar organizations around the world; some focused on specific aspects of pain, like neuropathic pain, and others on procedures and treatments of pain diseases. Publications, books, WebPages, and scientific and medical journals exclusively dedicated to pain research and management have flourished. We are living through a true revolution in the social perception of pain that has generated an unparalleled increase in pain research and has identified pain treatment as a social need.

**Advances in pain research**

Modern pain research began in the mid 1960s with the publication of the Gate Control Theory of Pain. Regardless of the scientific accuracy of the mechanisms proposed by the Gate Theory this seminal paper generated a considerable amount of research into the brain mechanisms of pain and switched the attention of scientists from the normal process of nociception to clinically relevant pain syndromes. In the decades that followed the publication of the Gate Theory much has been learned about the neurobiological properties of nociceptors, the neurons, and pathways that are activated by injury, the transmitters, and molecular mediators of nociceptive information and the brain areas that integrate injury related signals. It is impossible to synthesize in a few sentences the vast increase in our knowledge about pain mechanisms that has taken place in the last 40 yr but there are two areas that need highlighting: the development of experimental models of clinically relevant pain and the recognition that the plasticity of the nervous system is a key element in the generation of persistent and chronic pain.

Most of our knowledge on pain mechanisms has traditionally derived from laboratory studies that use brief noxious stimuli and very restricted injuries. This is unavoidable for obvious ethical reasons that take into account the need to treat animals humanely and the necessary restrictions of human experimentation. The drawback has been a lack of experimental studies of clinically relevant pain. Scientists have tried to approach this problem by developing animal models aimed at reproducing the circumstances of persistent and chronic pain but still remaining within ethically acceptable limits. Many models of persistent, inflammatory, and neuropathic pain have been described in the last decades and this has become an area of considerable activity in pain research not only as a way to approach clinical pain but also in search of potential biomarkers for the process of pain chronicization. The extent to which these models are validated by the development of new analgesic therapies remains, unfortunately, an open question.

Another major area of interest has been the study of the neuroplasticity of the nociceptive system. We know that pain is a dynamic sensation and we think that the symptoms associated with hyperalgesia are the consequence of plastic changes along the entire pain system, from the peripheral nociceptors, to spinal and supraspinal neurons and the higher centres of the brain. We believe that this process of sensitization is key to the understanding of chronic pain and of many clinically relevant conditions. However, a therapeutic link between neuronal sensitization and pain relief remains
to be established as much of the new knowledge gathered in search of this link relates to the basic principles of synaptic plasticity rather than specifically to pain.

Translating from the lab to the clinic

Ultimately, the aim of much of the basic research into pain mechanisms is to develop new and more effective pain relief therapies and in order to achieve this goal we must address some very substantial challenges. First of all is the question of the relevance of animal models to clinical pain: not only many of the models are based on simple and brief procedures but the significance of pain to a laboratory animal as opposed to a chronic pain patient is also a matter of debate. Then, there is the fact that we have had very powerful methods of pain control for a very long time, particularly the opiates, and it is very challenging to measure the effectiveness of new drugs against these powerful analgesics. There is also the question of the cognitive and emotional aspects of chronic pain, often the most powerful component of the persistent pain seen in the clinic, and difficult to assess in lab experiments. And finally, there is also the difficulty of measuring pain objectively in normal volunteers and in patients; we still depend mainly on verbal reports and subjective evaluations.

It is, therefore, not surprising that some spectacular failures have occurred in this translational path; one often-quoted example is the lack of analgesic properties shown by NK1 receptor antagonists in human trials in spite of a substantial positive literature from animal experiments. Some pessimism is detectable on the analgesia translational crowd and there is evidence of reluctance in the pharmaceutical industry to pursue this translational path. Time will tell whether this is a short-lived blip or a more permanent result of the complexities of lab to clinic translation in pain research.

From here to eternity

Predicting the future is a risky business but we can be fairly certain that the human enquiry into the workings of our brain will continue and that sooner or later we will gain a better understanding of the process of pain perception and therefore of how to alter and modify pain sensitivity. We know that this is no easy task but we are witnessing almost every day new advances in brain imaging—which may finally give us tools for an objective assessment of pain perception—and in pain genetics—which will provide insights into the process of pain chronification and offer ways for personalized analgesic treatment. We cannot be anything but optimistic in our quest to unravel pain mechanisms.

A different question is how the translational path from lab to clinic will be organized for this quest. The contribution of pharmaceutical companies is key but the industry is rapidly changing and is driven by economic factors beyond those purely scientific. It is very likely that some major transformations will take place in the immediate future in the relationship between industry and academia.

What is evident is that the social demand for better and more effective analgesia will be maintained or even increased. We still face huge deficits in basic analgesic procedures in the developing world and this can easily be solved with political will and organization. The social transformation that has taken place in the last decades is the leading force that drives scientists and clinicians to know more about pain mechanisms and to treat pain more effectively. Mankind has clearly decided not to suffer in silence and this social demand is very unlikely to be reversed.

Declaration of interest

None declared.

References