Scandinavian Journal of Pain 2 (2011) 130–131

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Editorial comment

Effects of the excitatory amino acid transporter subtype 2 (EAAT-2) transporter inducer ceftriaxone (an antibiotic) on different pain modalities in rat

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The article in this issue of *Scandinavian Journal of Pain* by Eljaja et al. [1] presents opportunities for discussion at several different levels, all of which cannot be covered in an editorial. I think that it is interesting to take a step back and to consider the motivation behind the article and the potential effects of this form of research from a broader perspective. The motivation for such research is based on a blend of cultural, societal, economic and intellectual interests.

Ceftriaxone is an enhancer of the GLT-1 mechanism that controls uptake of glutamate from synapses into central nervous system cells and therefore can reduce the amount of free glutamate available to stimulate transmission at NMDA receptors. One can wonder why the authors chose this mechanism to study. Down regulating glutamate induced activity in the nervous system as a mechanism to affect pain is not new. Up regulation of the glutamate/NMDA system is felt to be the primary process in secondary hyperalgesia, a form of central sensitization and a mechanism present in post operative pain [2] but central sensitization is also felt to be a major cause of many of the signs and symptoms of neuropathic pain [3]. Ketamine, which was introduced into anesthesia in the 60s (it was called CI581 in 1968 when I first used it) is not new and it is an ionotropic glutamate receptor antagonist. It has been used to treat acute post operative pain, fibromyalgia and refractory forms of neuropathic pain although with varying degrees of success [4–6]. The mGluR antagonists are metabotropic glutamate receptor antagonists and have been investigated for use in pain and depression for some years but are limited in use because of low efficacy and many of the side effects in common with ketamine and related compounds. So the search for modulators of glutamate activity has a long history.

But why do we continue to look at this mechanism? A part of modern scientific culture is reductionism [7–9]. We want to know as much as we can about all the possible neuron/receptor/transmitter mechanisms involved in pain; acute, chronic and cancer related. If we understand all of these and can control these processes, then we must be able to control pain. There is also the hope that every new mechanism will be the key to solve all pain problems – a single compound should be highly effective in all patients, is the thought.

Another reason that we are so driven is societal. We know that modern medicine is miraculous. New science can conquer all disease and pain is no exception. But, despite all the new knowledge, we have no truly effective treatments for neuropathic pain nor for many other forms of chronic pain. About 30% of those treated with the current first line drugs for neuropathic pain are 50% better [10]. Many patients are not satisfied with 50% better and if you are in the other 70% who have less effect, you are very dissatisfied. The basic thinking is that we are not looking at the right mechanism. Society says that if we find the right key to the primary process behind neuropathic pain, our problem will be solved. A new wonder drug will be born! What is wrong with this picture? Back to reductionism. The fact is that there are hundreds of mechanisms involved at the same time and different combinations of some of these are probably active in different patients with the same diagnosis. The reductionist view is doomed to failure in pain treatment as witnessed by the billions of dollars spent by “big pharma” who have not brought to market one new drug for pain that came from a basic science idea. All of the successful drugs have come from folk medicine, by serendipidy or by modification of old drugs. Society has bought into the reductionist view and has high hopes for the future. Society also demands perfect health and the pressure is on to deliver perfect pain relief.

Into this equation comes financial concerns. “Big pharma” knows that a medication that can only deliver 50% pain relief in 30% of patients is worth over one billion dollars a year in US sales alone. They search for new “blockbusters” and the “big pharma” funding drives both academic and commercial research but also demands a reward for this. The income from their products must pay for their basic costs but also must pay a dividend to the stockholders who need a financial return on their investment. Despite “big pharma’s” failure and a few very costly near misses recently such as tanezumab [11], the search goes on, but this search demands even greater and greater market value for new compounds as the costs escalate. Effective compounds for niche diagnoses are abandoned as not lucrative enough and some patient groups are deprived of medications that could be very helpful because of this. And the spiral continues.

On the academic side, the need for research funding is high but those who fund demand that articles be published to vindi-

DOI of refers to article:10.1016/j.sjpain.2011.03.003.
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1877-8860/$ – see front matter
doi:10.1016/j.sjpain.2011.05.003

cate their choices for financial support. This drives the machine and an increasing amount of academic researchers' time goes to grant writing and article writing, not to research. Scientific curiosity often is stiffled and more and more time is taken to polish papers for journals with a high citation index. Just as "big pharma" must satisfy their stockholders, academe must satisfy their stakeholders and academic researchers are under similar pressures to those in industry.

But in the end, the source of much research endeaver lies in scientific curiosity. This applies to both industry and academe since the best ideas often come from a curious mind that dares to be different and often will chose the path less taken because it leads to a tempting unknown that is the heart of true science. Despite the cultural, societal and economic pressures that cannot help but influence research, scientific curiosity is the magic that is the ultimate stimulus. I do not know the forces that shaped the research behind this article but it is a pilot project built on new and old ideas that focus on one small bit of the complexity of pain [1]. The hope is that this is a seed which has been planted now and that the next stage in its growth will add more pieces to the puzzle of pain.

And so, what do we learn from this article? We have some evidence from this pilot study that modulating the glutamate/NMDA system in rats with acute inflammation and in the acute phase of a neuropathic pain – like state can modify the behaviours that appear to be nocifensive. This could be a clue to a new treatment for pain in humans but we have a long way to go. First, these findings must be replicated in a larger study for reliable statistics. The evidence here is for a modest effect only and with a larger study, the true effect size can be better estimated. Due to the toxicity and the fact that ceftriaxone is for injection only, a useful place in clinical practice is not likely for this compound and a similar, more patient friendly compound will be needed. My bet would be that the clinical effect would not be sufficient to bring it to market since this is just another of the multitude of processes involved in pain. A more comprehensive approach with combined medications targeted on a specific patient's profile will ultimately be the most successful approach to the difficult chronic pain problems we are asked to treat.

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