Effective Electroceuticals

Central sensitisation is often seen as the physiological explanation for many neurological disorders, such as chronic pain. Electroceutical treatments may provide a non-invasive means of desensitisation

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Pain is a normal physiologic signal by which the brain communicates to an individual that tissues in the body are in danger or have already been damaged. Typically, when the tissue damaging agent is removed or the tissue heals, the pain subsides. However, sometimes, even long after the tissues have healed, the brain continues to sense pain – this is classified as chronic pain. More specifically, the International Association for the Study of Pain (IASP) defines pain as chronic if it lasts for more than three to six months (1). Chronic pain can manifest as musculoskeletal, neuropathic, or idiopathic, but, most importantly, it can significantly reduce quality of life due to both physical and emotional impacts on the individual. Chronic pain is remarkably prevalent, affecting up to 30% of the global population, reflecting a global therapeutic market that is expected to exceed US $83 billion by 2024, or approximately one-third the size of total current biopharmaceutical markets (2-3).

Currently, three main classes of traditional pharmacologic interventions (OTC and prescription) are used to manage pain: 1) opioids/opioid-like agents/opioid-analgesic combinations; 2) NSAID's/analgesics; and 3) adjuvant therapies such as anti-depressants, anti-convulsants, anti-rheumatics/immunologics, muscle relaxants, topical products, and corticosteroids. Biopharmaceutical approaches to pain management have not, to date, been extensively pursued. In part, this may be because biopharmacologic approaches tend to be more focussed on personalised therapies, and pain is often considered a generic healthcare challenge (4). However, recent developments in pain management suggest an opportunity for the development of targeted therapies, a strategy that may fit well with the biopharma industry's long-term goals (5).

Central Sensitisation

The neurophysiologic understanding of pain management is founded on the work of Melzack and Wall who introduced the Gate Control Theory in the mid-1960s (6). The commonly observed phenomenon of reducing pain sensation by rubbing injured tissue was explained in this theory as the ability of fast, sensory nerve fibers serving to block the activity of the slow, noxious nerve fibres. This theory quickly led to the development of transcutaneous electrical nerve stimulation (TENS) technology as a means to block pain and therefore provide a non-pharma approach to pain management. While it is not practical to 'rub' injured tissue continuously, an electrical stimulator using electrode pads on the skin to permit electrical current injection can readily be designed to operate for hours, thereby providing sustained pain relief. However, sustained electrical stimuli in and of themselves can be irritating, and, furthermore, high electrical current densities injected through the electrode pads can damage skin, so usage is typically limited to a few hours per day. As a result, TENS has played a limited role in pain management. A limitation of the Gate Control Theory of pain is its inability to explain chronic pain. In the mid-1980s, an extension of the theory was proposed – the Central Sensitisation Theory (7). This concept has been further developed by Melzack (one of the creators of the Gate Control Theory) into the Neuromatrix Theory of Pain (8). The premise is that pain is a multidimensional process, produced by patterns of new impulses generated by a widely distributed neural network, the 'body-self neuromatrix.' This neuromatrix can be modified by sensory experiences and learning, initiated by both peripheral and central neural activity that modulate the sensitivity of the neuromatrix to incoming stimuli. These physical changes most often occur when high levels of acute pain are sustained for an extended time period (7). This sensitisation leads to allodynia (increased sensitivity to non-painful stimuli), hyperalgesia (enhanced pain response to painful stimuli), and temporal summation (facilitation of centrally-mediated pain). These conditions are the essence of chronic pain. 'Central sensitisation' is commonly associated with pain conditions such as osteoarthritic knee pain, neck pain, low back pain, dysmenorrhea, fibromyalgia, myofascial pain, migraines, and painful bladder, among many others (9).

Complementing central sensitisation is habituation, the process by which sensation thresholds are raised. Sensitisation and habituation are normal physiologic processes that allow the nervous system to operate optimally. In the case of central sensitisation, the normal habituation/sensitisation process has been transiently disrupted (9). Nonetheless, central sensitisation does not appear to be a pathology, rather, the system has become stuck in a pain state. Recent research indicates that one effective strategy for achieving chronic pain relief (reversal of sensitisation) lies in providing sustained, sub-threshold (ie, non-sensed), information to the sensitised area (10). Correspondingly, long duration neuromodulation of peripheral nerves can serve as an ideal intervention for reducing chronic pain.

Electroceutical Development

Therapeutic neuromodulation is defined as "the alteration of nerve activity through the delivery of electrical stimulation to targeted sites of the body" (11). While stimulation to the point of sensation requires semi-invasive techniques, such as TENS, sub-threshold stimulation can be achieved using non-invasive techniques, such as electromagnetic field exposure (12). As a class of healthcare devices, these various approaches have come to be known as electroceuticals. Electromagnetic field (EMF) stimulation has the distinct advantage among electroceuticals of being able to produce effective stimulation through bandages, clothing, insoles, etc. Moreover, EMF neuromodulation devices are incapable of producing electrical shocks or uncomfortable

sensations during use and are well-accepted by patients (13). Finally, the low levels of EMF stimulation required to achieve neuromodulation permits the development of devices with very long battery lifetimes.

Pulsed shortwave therapy (PSWT) devices utilise pulsed, high-frequency EMF to modulate nerve activity. The mechanism of action is believed to be based in quantum biological processes, specifically, by influencing free radical lifetime in protein signaling complexes (14). This biological basis suggests that this newly developing field of neuromodulation may be of particular interest to the biopharma industry as the opportunity exists to create specific pulsed EMF pattern to regulate specific biochemical pathways. Alternatively, there is the potential to create products that can be adjusted to the specific tissues being treated, resulting in a type of personalised therapeutic application. Additionally, opportunities exist to develop biopharmacologic products that work synergistically with EMF therapies. PSWT devices have already been demonstrated to provide benefit for individuals with a variety of chronic pain conditions such as that associated with knee osteoarthritis, plantar fasciitis, musculoskeletal (low back pain, shoulder tendonitis, etc), and non-musculoskeletal chronic pain conditions (13,15-17). Nonetheless, the field of electroceuticals is young, and much remains to be learned. That PSWT provides a local, controlled therapy that can be customised to influence specific pain pathways or, alternatively, to adjust to specific tissue characteristics, suggests that that this technology may play a critical role in the future of pain management. Given the anticipated tremendous growth rate of the pain management market, further R&D of this technology can be expected.

Final Thoughts

Chronic pain is a highly prevalent condition that significantly affects quality of life. Pain research has demonstrated that central sensitisation or neuromatrix hypersensitivity induced by sustained pain is a causal factor of chronic pain. Current pharmacological therapies have limited effectiveness, while presenting potentially significant side effects with long-term use. An effective adjunctive pain therapy, which can be used to complement pharmacologic treatment strategies, could reduce the risk of adverse interaction of pain medication with other drugs, food, and/or existing medical conditions, as well as the risk of addiction. Traditional electroceutical medical devices can provide acute pain relief by masking through targeted neuromodulation, but typically require invasive or semi-invasive use, so treatment durations are limited. PSWT technology is a type of electroceutical technology that is non-invasive and utilises high-frequency EMFs to achieve neuromodulation without producing uncomfortable sensations during use. The versatility and economic advantages of this technology mean that it has the potential to treat a wide variety of chronic pain conditions. Most importantly, PSWT operates through normal biological processes to raise the pain sensation thresholds towards normal levels. This mechanism of action sets the stage for development of a variety of biopharmacologic products that could work in synergy with PSWT technology.

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