Chronic Pain and Management Journal
Clayton P. Chron Pain Manag 6: 146.
www.doi.org/10.29011/2576-957X.100046
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Mini Review

Can Chronic Pain be considered a Disease of Civilization?

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Citation: Clayton P (2022) Can Chronic Pain be considered a Disease of Civilization? Chron Pain Manag 6: 146. DOI: 10.29011/2576-957X.100046

Received Date: 17 October 2022; **Accepted Date:** 31 October 2022; **Published Date:** 04 November 2022

Abstract

The increasing incidence of chronic neuropathic, neurogenic and nociplastic pain, together with decreasing latency and the role of neuroinflammation in pain perception, all suggest that the modern diet and lifestyle is adding considerably to the overall burden of pain and the growing need for adequate pain management. These same factors dysregulate the body's endogenous pain modulating endocannabinoid and immune systems. Novel dispersant technology now allows the use of certain endogenous agonists as therapeutic tools with uniquely high therapeutic indices.

Keywords: Pain management; Pain matrix; Neuropathic; Nociplastic; Nociceptive; Neuroinflammation; Palmitoylethanolamide; Autacoid

Access to pain management is considered a fundamental human right [1], but safe and effective pain management is still, for many, little more than an aspiration. In the United States over one in four adults suffers from chronic pain [2], and the drugs used to treat pain leave much to be desired. The peptic ulcer and cardio problems linked to NSAID's [3], and the public health crisis caused by the over-zealous marketing of opioids, have damaged confidence in the prevailing medical model.

Has Life Always Been so Painful? [4]

AActually, no. The prevalence of chronic pain has increased significantly during the last two decades [5,6], currently affecting 20% of US adults [7] and a significantly higher percentage of older adults [8]. This Janus finding shows that external factors are affecting the neurological and immunological substrate of pain, and that their identification could lead to new treatment and prophylactic strategies. The fact that even among children the incidence of chronic pain is now, startlingly, over 10% [9], makes this quest all the more urgent.

Might our diet be causing this? Is the fleeting pleasure of ultra-processed food making our lives more painful? And if so, would restoring pre-transitional nutritional values help?

Within the USA there is evidence suggesting that chronic pain is more likely to affect folk who eat a more ultra-processed and pro-inflammatory diet [10-12], and those with lower socioeconomic status [13,14], linked to poorer diet. When one examines global patterns of ultra-processed food consumption [15], however, it is hard to make out any broader trend.

Europeans eat a more traditional diet, and their chronic pain figures are lower than in the USA [16]. The British and Japanese also consume less ultra-processed food than Americans, yet their recorded chronic pain figures appear to be somewhat higher [17,18].

The fact that the data are not particularly coherent is unsurprising. The studies used different survey methods and different pain criteria. None of them attempt to distinguish between the three main sub-types of chronic pain (neuropathic, nociceptive and nociplastic), which respond differently to dietary inputs. And pain does not occur in a neurological vacuum; its perceived intensity is affected by interwoven social and psychological factors which differ in different individuals, families and cultures.

For example, individuals with chronic pain typically have higher psychological distress scores [i.e. [17]]. It is a bi-directional relationship. Chronic pain is stressful and may reduce opportunities for social interaction. Conversely, social pain [loneliness, social defeat, anger] tends to exacerbate physical pain, especially nociplastic pain [19, 20], probably by activating a shared neural network known as the pain matrix [20-22].

The pain matrix is sensitized by early life trauma [23] and amplified by neuroinflammation [24], which is affected by multiple

lifestyle factors.

Transient low-level neuroinflammation is physiologically normal, and entirely positive. It is involved in immune surveillance and signaling, together with aspects of brain development, memory and learning [25,26]. At higher levels, it is a crucial element in injury repair.

If neuroinflammation is excessive and/or chronic, however, triggered by a pro-inflammatory diet and/or substantial peripheral inflammation, or by repeated social defeat, it gives rise to sickness behaviors including loss of appetite, lethargy, apathy, demotivation, reduced activity and reduced sociability [27]. It also drives depression, brain ageing and neurodegenerative disease [27,28]. (28 is a fascinating and comprehensive read).

Our rising intakes of pro-inflammatory, ultra-processed foods, which drive inflammatory disease, will therefore contribute to increasing reports of chronic pain [27,28]. Progressive damage to our social networks and repeated social defeat will add to those numbers [29,30].

There are rare individuals with genetic factors that leave them unable to feel pain [31]. This raises the question of whether such individuals might also be immune to solitude and social defeat [22,23], but this appears not to be the case [32]. We are more complex than that [33] … and being pain-free comes with its own set of problems. It would be better to have a more moderately skewed genetic makeup, which reduces but does not abolish the likelihood of chronic pain, and depression [34,35].

Interestingly, two UK Biobank studies [34,35] found significant genetic differences in male and female pain-associated SNP's. This may be one of the reasons why women generally experience more recurrent pain, and likely experience more severe pain and longer-lasting pain than men do [i.e. 36,37].

An increasingly pained society provides a healthy market for painkillers, but this is not a healthy response. Already well known to cause health issues, evidence is accumulating that they may actually be counter-productive.

Pain, inflammation, the immune system, nutrition and healing are all intimately connected. Inflammation following injury is an essential part of the process of tissue remodeling and repair [38], and there is some evidence that if drugs are used to suppress inflammation after injury, healing may in some cases be slowed [39]. New research suggests that inflammation also re-sets local neural networks so that the acute pain of injury fades as the wound resolves; and that anti-inflammatory drugs may disrupt this too.

A research team out of McGill University [40] examined 98 patients with acute injury and found that when innate immune cells known as neutrophils were inhibited by NSAID's or steroids, pain was almost twice as likely to become chronic, and last up to 10 times longer than in controls. Acetaminophen and lidocaine, which reduce pain without damping neutrophil activity, did not have this effect.

To add insult to the original injury, the Cochrane Collaboration finds that the NSAID's are only marginally effective in the management of acute [41] pain, and barely effective at all in chronic [42] pain. Overall, therefore, the case for anti-inflammatory analgesics in the management of chronic pain is looking very shaky.

There is a compound produced in the body in response to injury, which may be a more appropriate therapeutic tool. This is the autacoid palmitoylethanolamine (PEA), a quasi-endocannabinoid which acts as the body's first response to tissue damage, pain and inflammation.

PEA is formed locally where and when needed, and modulates the neuronal transmission and sensation of pain [43]. It is effective in many models of neuropathic pain including surgical [44], diabetic [45] chemotherapeutic [46], and compression [47]; and in nociceptive [inflammatory] pain also [44].

The Montreal group found that neutrophils exerted analgesic effects where and when needed, and PEA operates in precisely this manner. Neutrophils appear to act in conjunction with local PEA synthesis whenever the body responds to injury, but the collaboration is a complex one.

PEA's anti-inflammatory effects include inhibiting neutrophil migration into areas of tissue damage [45-47]. Theoretically, therefore, PEA should slow recovery from pain. This seems counter-intuitive, and the available evidence suggests that it does not happen. PEA appears to accelerate the repair of micro-damaged tissue (i.e. [48-50]).

We need to think in subtler terms, and re-thinking neutrophils could be the key. Neutrophils, once thought of as simple phagocytic cells that drive inflammation, are now known to play many other roles including a final interaction with macrophages which enables the resolution of inflammation [51]. There appear to be multiple sub-types of neutrophil which are induced and/or transformed in different tissues as and when required [52].

The fact that PEA reduces neutrophil infiltration after injury, and yet does not delay pain or damage resolution, suggests that it acts selectively on neutrophil sub-types in a functional and adaptive manner.

PEA's evolutionary complexity and fitness for task is confirmed by its ability to shift macrophages into anti-inflammatory and pro-resolving mode [53], which dying neutrophils also do

[51]; and to prevent mast cell degranulation [54-56] by blocking Substance P [57], a neuropeptide produced by tissue damage, which modulates pain perception. It exerts additional anti-inflammatory and anti-nociceptive actions via selective activation of PPAR-alpha [58] and CB1 [59] receptors; and may play a pivotal role in preventing the transition from acute to chronic pain [58,60]. Finally, by reducing neuroinflammation, PEA alleviates [pre-clinical] anxiety [i.e. 61], and [clinical] depression [62].

The above data suggest that PEA synthesis might be usefully considered as a component in the cell danger response. How does this relate to the recorded increase in cases of chronic pain?

Pain and inflammation after injury is normal and desirable. Our bodies need to learn what is harmful, and to defend against intruders. Neutrophils are involved in pain and inflammation, and under 'normal' metabolic circumstances (i.e. when we were still eating a pre-transitional diet), presumably appropriate numbers of the right neutrophils were engaged.

The industrial, pro-inflammatory diet likely skews cellular and autacoidal responses to injury (i.e. 63-65), increasing the chances of progressing to chronic inflammation and pain - which is what the epidemiology shows is happening [5,6]. And when pain and inflammation are protracted, as they are by the modern diet [63-65], PEA 'exhaustion' may develop: chronic inflammatory conditions eventually reduce the body's ability to generate PEA [55,56].

Even this is not the end of the story, because the modern diet also causes dysbiosis. The gut microbiome is involved in pain sensing, and in inflammatory, neuropathic and nociplastic pain sensitization [66-72]. The enteric nervous system probably evolved before the CNS [73], there is considerable cross-talk between the two and the dysbiosis that is so common today is likely contributing to the increasing numbers of individuals who reportedly graduate from acute to chronic pain [5-7].

Chronic pain appears to lead to increased connectivity in the pain matrix [74] via a learning or kindling effect which may well be exacerbated by neuroinflammation [24]. The pain matrix communicates with the default network, which is functionally altered during the experience of pain, may be structurally altered by chronic pain [75] and is also degraded by the modern diet [76].

Chronic pain also affects the salience network [77], which overlaps with the default network in the cingulate, potentially explaining how the intensity of perceived pain can be modified by distraction; and why pain is worsened by loneliness [19,20].

Here is a neurological substrate that links social emotions, emotional processing, self-image and pain perception. It implies that as Western society continues to fragment, our self-worth continues to be attacked and our diet continues to deteriorate, chronic pain will become an unwanted guest in ever more homes. We will tend to focus more on the negative aspects of our lives and experiences, driving isolation, depression and anxiety [78-81] and immune dysfunction [82-84] in a descending spiral.

What are the Implications for Medical Practice?

The pain matrix appears to be down-regulated by antidepressant drugs such as duloxetine [85], which has some ability to reduce neuroinflammation [86,87] and relieves physical pain more rapidly and more effectively than it does mental distress. Duloxetine's withdrawal effects, unfortunately, can be seriously problematic.

I revert to the body's endogenous analgesic, PEA. With excellent safety data [88,89] and efficacy in numerous models of pain [43,45-48,89-91], it has recently been found to reduce inflammatory markers and stress in athletes [50] and in Covid patients [92]. Non-addictive and free from withdrawal effects, it attenuates cocaine cravings in pre-clinical models [93] and is currently being trailed for opioid reduction in below knee fracture fixation [94].

Due to its ability to reduce neuroinflammation [56,61,95], palmitoylethanolamide has also found uses as a sleep aid [96] and mood enhancer [97].

PEA's main barrier to use has been its poor oral bioavailability. Micronised preparations made some progress in this direction but the issue has recently been resolved by Lipisperse™, a novel delivery system that uses cold water dispersion technology to dramatically enhance the bioavailability of hydrophobic agents [98]. When given as a supplement, PEA- Lipisperse™ likely acts not only at the site of injury but also within the pain matrix, in a non-autacoidal manner.

This old / new analgesic should now be reconsidered as a physiologically appropriate first line intervention in pain management.

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