Editorial

Key mechanisms mediating fibromyalgia

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Fibromyalgia (FM) is characterised by an unusual distribution of widespread pain and a constellation of symptoms and comorbidities. Prominent symptoms include increased pain sensitivity to blunt pressure, heat and other pain modalities, and increased sensitivity to non-painful sensory stimulation such as sound and smell. Patients report cognitive difficulties, and cognitive deficits are found with objective testing. Other complaints include morning stiffness and non-refreshing sleep. Fibromyalgia may occur in isolation but is usually accompanied by a number of comorbid conditions that include chronic fatigue, irritable bowel syndrome, temporomandibular disorders, migraine, and vulvodynia (1). There is general agreement that individuals may be predisposed to develop this disorder by genetic and environmental factors, and that the condition may be precipitated by a stressor (2-6). However, little is known about the mechanisms that can account for symptoms of widespread pain, cognitive confusion, disordered sleep and enhanced sensitivity to both painful and non-painful stimulation.

In an attempt to explain these symptoms, numerous authors have described FM as and example of central sensitisation or a "central sensitivity syndrome" (CSS). This choice of nomenclature is possibly confusing because the term "central sensitisation" has been used to describe a specific condition that is quite different from fibromyalgia. However, details of central sensitisation are instructive and provide an example that may help define the true nature of FM.

Pain clinicians encounter patients with puzzling symptoms of spontaneous pain and evoked abnormalities such as mechanical allodynia and pin-prick hyperalgesia. While these symptoms have been known to prompt a diagnosis of hysteria and a referral to a psychiatrist, subsequent evidence provides a simple physiological explanation to this puzzle. We now know with certainty that focal input from nociceptors due to injury or other sources such as a neuroma can activate a spinal process of central sensitisation that produces spontaneous pain and evoked symptoms that extend beyond the region of injury. These regions of pain and sensitivity to light brushing, pin prick and cold can include an entire limb and include multiple nerve territories. Almost magically, all of these symptoms may vanish after local anesthesia of a discrete region that is responsible for the persistent nociceptor input (7). For example, an afferent barrage from a superficial neuroma associated with a surgical incision is a likely source of nociceptor input that initiates and maintains symptoms. Infiltration of just a drop of local anesthetic at the knee or ankle can abolish pain and symptoms in the entire lower leg (7).

It is now very clear that spinal central sensitisation represents an intricate neurophysiological programme that exacerbates pain. It serves an important purpose. Following injury, this exacerbation alters behaviour, promoting quiescence and a posture that protects and immobilises the injured region. This effect is recuperative, it promotes natural healing. It can be described as a protective programme with a regional focus centered on an injury or other pathological process. Thus, as noted years ago by Wall (8), we can distinguish between pain that evokes movement (to minimise or avoid injury) and pain that inhibits movement (to maximise healing).

What is also clear is that research studies on the consequence of this programme, such as the extent and nature of allodynia, reveal little about the pathology that activates this programme. As shown in Figure 1, diverse inputs such as inflammation, nerve injury or

sympathetically maintained pain may funnel to a common final pathway that activates an intrinsic system that results in a coordinated response that includes widespread pain and sensory symptoms. In contrast to the typical pain response that evokes movement to avoid or minimise injury, this recuperative system inhibits movement to promote healing. These symptoms are designed to exert an effect. They are part of an integrated programme activated by pathology, but not a direct consequence of pathology. One cannot learn much about the pathology by studying details of the system response. Similarly, attempts to link a putative pathology directly with the output of the integrated programme is doomed to failure. For example, what feature of a neuroma would lead directly to widespread pain in multiple nerve territories and sensitivity to light brushing and pin prick in adjacent, healthy skin? In Figure 1, the inputs do not interact directly with the outputs. The action is through an intermediate activation of an innate programme designed to promote normal function by activation of reflexes and motivation of behaviours that in this case promote and protect restorative processes.

Recuperative and protective mechanisms are common biological systems. Such systems were the focus of Cannon's classic "Wisdom of the Body" (9). These include "homeostatic" mechanisms that maintain a homeostatic neutrality by both physiological processes and overt behaviour. A prime example is thermoregulation, in which physiological processes of vasoconstriction and shivering act to maintain core temperature in cold environments and vasodilation and perspiration act similarly in warm environments. These physiological mechanisms are supplemented and even preceded by unpleasant feeling states that motivate behaviour to reduce unpleasantness and seek pleasantness. Humans and animals seek a sunny part of the room if cold and adapt postures to conserve heat. Humans can also put on clothes and create warm environments.

Thermoregulation is an interesting example of a bivalent mechanism that regulates departure of core temperature in either direction. Many other regulatory mechanisms serve as "gas gauges," restoring levels depleted by biological processes, such as thirst and hunger. Probably the most intense feeling state is associated with a system that needs to be tightly regulated. Our survival depends on the regulation of internal acid-base balance, which we regulate by exhaling carbon dioxide. This system requires both precision and immediate adjustment. Thus, the feeling state that motivates behaviour is an aversive sensation that quickly escalates to include feelings of fear and panic.

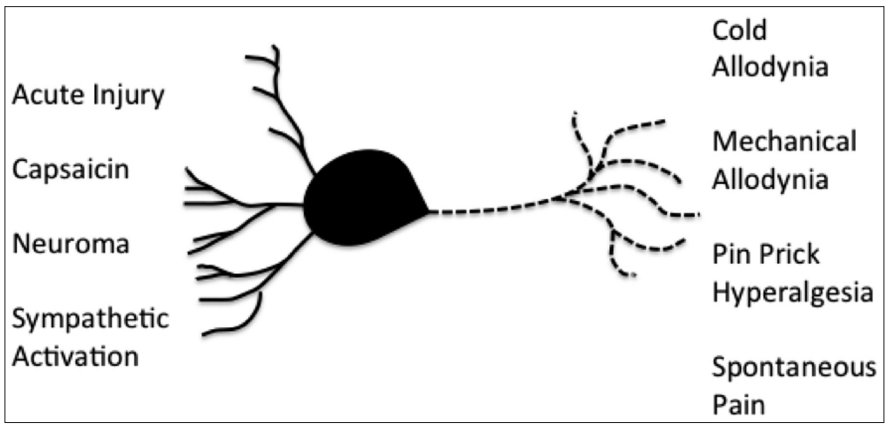

Fig. 1. Various types of inputs from nociceptors can initiate a process of central sensitisation that results in groups of symptoms that include cold allodynia, dynamic mechanical allodynia, pin prick hyperalgesia and spontaneous pain. These symptoms extend beyond the region of injury or stimulation and are perceived in adjacent intact tissue. This process is in part a neural spinal programme sympolised by the intervening neuron.

In addition to these homoestatic systems, Cannon elegantly described other systems that protect us from assaults. He is poetic in his descriptions of physiological defenses against foreign invaders, such as the beauty of a pimple. He applied the same awe to the coordinated reflex actions involved in a cough or a sneeze. Similarly, Cannon described the important sequence of events triggered by a potential toxic agent entering the stomach; feelings of nausea are accompanied by increased production of saliva in the mouth and of mucous in the gastric wall, diluting the contents of the stomach and facilitating the subsequent discharge. Respiration increases while the stomach is "quite relaxed." Abruptly the glottis closes and the diaphragm descends, resulting in an inability to breathe. These effects reduce thoracic pressure, dilating the oesophagus. The abdominal muscles contract violently and the esophageal sphincter opens, forcibly ejecting the contents of the stomach while protecting the airway from aspiration.

These effects yield an important concept. Similar to the consequences of a neuroma, the toxin that induces vomiting does not exert independent effects on the salivary glands, glottis, diaphragm and abdominal muscles. Rather, it triggers a programme that must precisely coordinate these events. Studying the effects of this programme does little to inform about the chemical characteristics that activate this programme. Similarly, the difficulty in identifying the mechanisms that mediate fibromyalgia may be due to a fundamental misconception about the locus of FM pathology. Searching for a pathological process that can account for the diverse features of widespread pain, confusion and hyperalgesia is likely pointless. These features do not represent the consequences of the cause but rather various aspects of an orchestrated response that is evoked by the pathological process. Figure 2 describes the key features of this model. A wide variety of factors may contribute to a final common pathway that activates a response system that results in the observed diverse symptoms. The right side of this FM "neuron" represents the activation of a neurohumoural programme that is responsible for qualitatively different symptoms. This system is activated by a signal that is in turn promoted by a

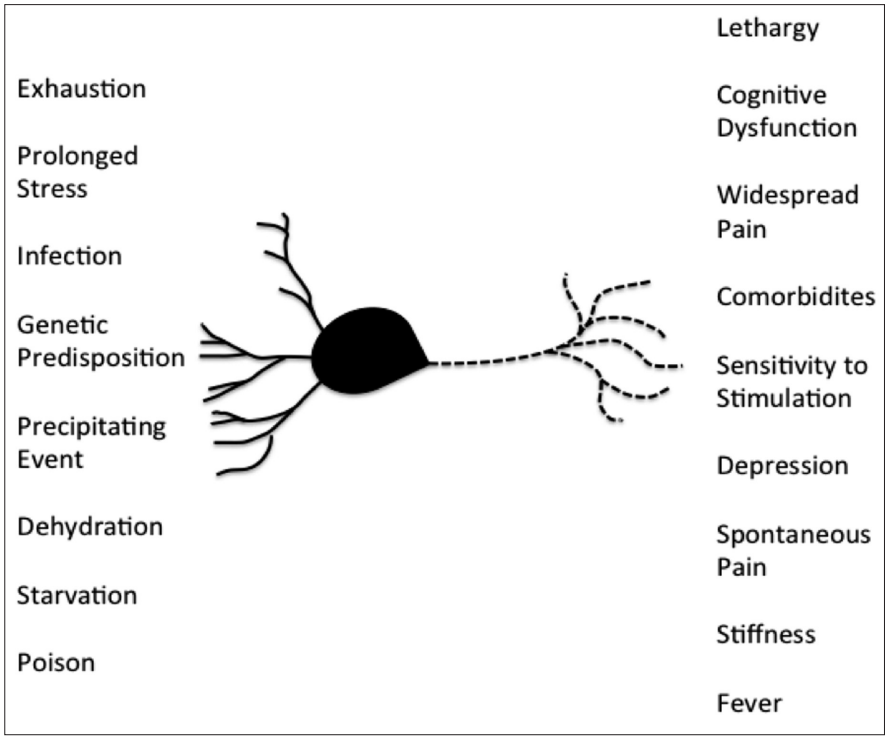

Fig. 2. The right column shows constellations of symptoms that are present in many clinical conditions that are associated with terms in the left column. The associations between symptoms and the commonality among numerous antecedents are hypothesised to represent the activation of an intervening programme represented by the schematic neuron. This programme and similar programmes have a behavioural purpose. They are designed to motivate specific behaviours, in this particular case the inhibition of most behaviour. The symptoms promote inactivity to promote survival in possibly critical situations. This quiescence programme may be truly needed, or once truly needed but failed to rest, or activated conservatively or inappropriately.

number of diverse inputs. The specific input and output arms may vary among individuals and may be influenced by genetic and environmental factors. However, all share the central feature of a central activation of this complex response system.

So what is the purpose of the programme that mediates the symptoms of fibromyalgia? In contrast to the regional protective programme of central sensitisation, this programme is a generalised alarm designed to stop all activity, to crawl into bed and rest. It signals an imbalance that may be augmented by further activity, increasing the difficulty of corrective action. Variations of this programme may be evoked during diverse conditions such as viral assault, acute poisoning or other disturbances in homeostatic balance. Features of this programme may be experienced while sick in bed with the "flu" or sick in bed with a "hangover" after a night of excessive alcohol consumption. In each case the symptoms promote behaviours that maximise restoration of normal function.

This concept is not new, originating largely from the work of Cannon, Bernard and Selye (9-11). Miller (12) showed that sickness behaviour was actually a purposeful motivational state and Hart (13) reviewed the evidence that sickness behaviour is not reactive but rather motivates behaviours that facilitate recovery. More recent investigators including Dantzer, Kelley and Johnson have delineated the sequence of events from infection, to immune response, activation of cytokines and physiological responses such as fever and behavioural responses such as sleepiness, lethargy, reduced hunger and thirst that facilitate recovery (14-18). Watkins and Maier broadened the cytokine effects to include hyperalgesia, mediated by the immune system rather than by the neural system (19). This body of work from the above investigators has focused on the response to infection, including fever (20). As shown in Figure 2, infection is but one of many possible triggers of the symptoms commonly associated with fibromyalgia. Others could include exhaustion, prolonged stress, dehydration, starvation, poisoning, and the important combination of a genetic predisposition and a precipitating event.

If we accept that the symptoms of fibromyalgia represent aspects of a programme with a purpose, the important questions ignore symptoms and ask how and why this system is activated and why the symptoms persist. In terms of Figure 2, the important research target is interaction between the input legs and the activation of the intrinsic programme.

In summary, this concept of activation of an innate programme is quite different than symptoms that result directly from pathology. Such concepts of a *reactive* physiological response are in sharp contrast to a *proactive* programme that orchestrates an ensemble of responses for a specific motivational/behavioural purpose. Both reactive responses and proactive programmes may contribute to symptoms. However, the focus is often on reactive responses, not on activation of intrinsic programmes. Such programmes are common and their presence in fibromyalgia cannot be ignored.

If many of the symptoms of fibromyalgia do represent the effects of a coordinated, programmed response then it is clear that investigating manifest symptoms symbolised by the outputs will do little to inform about the pathology that activates the system. It is analogous to the classic case of dropping keys at night and looking for them under a streetlight. The light illuminates an obvious area to investigate, but the key is elsewhere.

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