Focus Article

What Is Spontaneous Pain and Who Has It?

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Abstract: Spontaneous pain is often discussed in the context of both chronic inflammatory and neuropathic pain conditions, and it has been suggested that spontaneous pain, rather than stimulus-evoked pain, may be the more significant clinical problem. The following issues are discussed here. First, it is suggested that the concept of spontaneous pain makes no sense when the pain is the result of an ongoing inflammatory reaction. Evidence is reviewed that indicates that spontaneous pain is present in patients with neuropathic pain, but perhaps only in a subset of such patients. Second, it is suggested that in the presence of allodynia and hyperalgesia, stimulation from the activities of daily life occurs very many times a day and that these stimulus-evoked pains may summate to give a fluctuating level of daily pain that both patients and investigators mistake for spontaneous pain.

Perspective: Which is more important—stimulus-evoked pain or spontaneous pain? This review suggests that to answer the question we will need to distinguish neuropathic spontaneous pain from inflammatory ongoing pain and to differentiate both from summated allodynic and hyperalgesic pains caused by the stimuli of daily life.

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Key words: Allodynia, central sensitization, hyperalgesia, inflammatory pain, ongoing pain, spontaneous pain, summated pain.

When we think about pain mechanisms, we make a distinction between spontaneous pain and stimulus-evoked pain. The meaning of stimulus-evoked is self-evident, but the purpose here is to show that the meaning of spontaneous pain is not. This is not just a problem of semantics. It has practical consequences. For example, if we are to discover the cause of one thing, then it is of importance to clearly distinguish it from other things and to give different things different names. Furthermore, it has been suggested that research with animal pain models may not be clinically relevant because we may be assessing the wrong thing—stimulus-evoked pain—while the major clinical problem is spontaneous pain.

This objection rests on the assumptions that we know what we mean by spontaneous pain and that we and the patients can clearly differentiate between it and other types of pain.

These assumptions may be false for the following 3 reasons: 1) We often use the term spontaneous pain to refer to the fluctuating level of daily pain that is reported in both inflammatory and neuropathic conditions. As described below, spontaneous pain makes no sense in the context of an ongoing inflammatory reaction; the term makes sense only in the neuropathic context. 2) Spontaneous pain may often be stimulus-evoked pain, where the stimulus goes unrecognized because it is generated by the activities of daily life (both external stimuli and the internal stimuli that are produced by normal physiological processes). 3) In the presence of allodynia and hyperalgesia (in both inflammatory and neuropathic conditions), stimulus-evoked pains from the activities of daily life occur many times per day. We are overlooking the possibility that these pain episodes summate over the course of the day to produce a fluctuating level of persistent pain that is mistaken for spontaneous pain.

Definitions

When we say spontaneous pain we do not mean miraculous pain, ie, pain without physiochemical cause. The
International Association for the Study of Pain Task Force on Taxonomy does not give a definition for spontaneous pain. Recourse to the dictionary finds several meanings for “spontaneous.” The 1 meaning germane to this discussion is “Occurring without apparent external cause; having a self-contained cause or origin” (Oxford English Dictionary). The definition highlights the problem. First, “apparent” is a very odd word—it has 2 contradictory meanings: “true, by virtue of the evidence of the senses,” and “false, despite the evidence of the senses.” Second, the referents for external and self-contained are not specified.

Is Spontaneous Pain Present in Inflammatory Conditions?

Consider the following 4 examples:

(1) Is a toothache spontaneous pain? It has a self-contained cause and origin within the body—an infected tooth pulp. One might argue that bacteria are the cause of the pain and that these are (or at least at some time were) external to the body. But this is obviously wrong: bacteria do not cause pain—it is the inflammatory reaction to bacteria that causes pain.

(2) Is the pain from a peptic ulcer spontaneous? A peptic ulcer is associated with a more or less continuous burning or aching pain beneath the sternum. It is due to an inflammatory erosion in the mucosal barrier that allows gastric acid to reach the underlying tissue’s nociceptors. The cause of the pain, gastric acid, has an origin within the body.

(3) Is the pain that you feel after hitting your thumb with a hammer spontaneous pain? We will all agree that the initial pain is stimulus evoked. But if you hit your thumb hard enough it would hurt for hours or days. This persistent pain is the product of an inflammatory reaction to a sterile tissue injury. We can be certain that at some point in time, the pain ceases to be stimulus evoked and begins to be inflammatory.

(4) In the preceding examples, there is an obviously severe inflammatory process driving the pain, but there are chronic pain conditions in which the inflammatory process is more subtle. For example, not too many years ago, there was a debate as to whether osteoarthritis (OA) was an inflammatory condition. We now know that there is an inflammatory process (for review, see48), but it is more subtle than the fulminating inflammatory process that yields a red, hot, and swollen joint in the rheumatoid arthritis patient. So, is the daily pain reported by a patient with an osteoarthritic joint spontaneous pain? The cause originates within the body: an inflammatory reaction to a sterile tissue injury (degradation of the joint tissue).

In the 4 examples given above, the pain occurs during an inflammatory reaction and the cause of the pain can thus be said to be internal and self-contained with respect to the body. Nevertheless, we should not call this spontaneous pain. Indeed, we are often reluctant to do so and instead call it inflammatory pain or ongoing pain. I think that this is an implicit acknowledgement that the pain is evoked by a stimulus—the action of the products of inflammation on nociceptors. We should adopt the term “ongoing pain” for conditions in which there is an ongoing inflammatory stimulus that drives the pain. “Inflammatory pain” would be more generic because it would logically include ongoing pain, allodynia, and hyperalgesia.

When we say spontaneous pain, what we really mean is pain due to changes that are internal and self-contained, not with respect to the body but rather with respect to neurons in the somatosensory system. Spontaneous pain thus defined is absent in inflammatory conditions but present in at least some patients with neuropathic pain (see below).

Do Primary Afferent Sensitization, the Activation of Sleeping Nociceptors, or Central Sensitization Account for Inflammatory Ongoing Pain?

One might object to the foregoing conclusion and argue that inflammatory pain conditions are associated with changes intrinsic to neurons and that these are potential sources of ongoing discharge that might account for spontaneous pain. There are 3 such phenomena—primary afferent sensitization, the activation of sleeping nociceptors, and central sensitization. However, there is no evidence to suggest that any of these is likely to be directly responsible for inflammatory ongoing pain.

Primary Afferent Sensitization

The allodynic and hyperalgesic responses of sensitized primary afferent nociceptors are unquestionably due to changes that are intrinsic to the neuron. However, to the best of my knowledge, there are no demonstrations that the ongoing discharge seen in sensitized nociceptors is due to an intrinsic change. Such discharge appears to be due entirely to substances (inflammatory mediators) that are released into the tissue innervated by the nociceptor. The discharge is ongoing because of the ongoing presence of pain stimuli. All such substances activate normal nociceptors; ie, the response to inflammatory mediators is not due to an intrinsic change in the nociceptor that produces a de novo response to an inflammatory mediator.

Aspirin relieves the pain of OA because it blocks the arachidonic acid cascade and removes the ongoing stimulation of inflammatory mediators that drives the pain. Other chronic inflammatory pain conditions may have ongoing pain due to several mediators arising from different kinds of inflammatory reactions. For example, the ongoing pain of a joint affected by rheumatoid arthritis is blocked by aspirin and inhibitors of tumor necrosis factor alpha.

The only de novo response to chemicals in nociceptors that I know of is the evidence for the acquisition of a response to norepinephrine. This response is believed to be prominent in at least some patients with complex regional pain syndrome (CRPS), but there is no evidence...
that it plays a prominent role in other pain states. Primary afferent neurons in the normal rat express alpha-adrenoceptors but do not respond to norepinephrine. However, they do discharge in response to norepinephrine after nerve injury. This suggests a possible intrinsic change in the nociceptor, one that now depolarizes the cell upon the activation of a receptor that is normally expressed in a functionally inactive state.

**Sleeping Nociceptors**

In the normal condition, a large percentage of C-fiber nociceptors can be detected via their response to an electric shock, but they do not respond to a naturally noxious mechanical stimulus. These nociceptors are activated by inflammation. The relation between activation of sleeping nociceptors and primary afferent sensitization is not clear. For the purposes of this discussion they are considered to be different phenomena. The intrinsic changes that activate sleeping nociceptors are clearly capable of contributing to allodynic and hyperalgesic responses, but there are no data to suggest that the ongoing discharge of an activated sleeping nociceptor is due to anything other than the presence of inflammatory mediators.

**Central Nervous System (CNS) Changes**

Central sensitization is due to changes intrinsic to the pain-responsive neurons of the spinal cord dorsal horn (and perhaps other places in the CNS). Central sensitization clearly contributes to abnormal stimulus-evoked pains (allodynic and hyperalgesic pain), but there are no demonstrations that central sensitization produces an ongoing discharge in nociceptive CNS neurons that is independent of primary afferent input.

**Is Spontaneous Pain Present in Neuropathic Conditions?**

Yes, in at least some, but perhaps not all, cases. It is due to an intrinsic change—the acquisition of spontaneous discharge—in primary afferent nociceptors and/or in nociceptive CNS neurons. There appear to be several phenomena that may generate spontaneous discharge in the neuropathic condition.

**Instability of the Axonal Membrane**

We have evidence from both humans and animals showing that axotomy can produce spontaneous discharge in primary afferent neurons (for reviews, see). The intrinsic changes that produce this spontaneous discharge are not known with certainty. After a traumatic nerve injury, afferent neurons with spontaneous discharge of high frequency (several tens of impulses per second in A-fibers) also display small, spontaneous, sinusoidal oscillations in their axonal membrane potential. The role of these oscillations in the genesis of the spontaneous discharge is not completely understood. At the resting potential, the oscillations yield depolarizations that are too small (~5 mV) to generate a nerve impulse. Some other factor or factors must partly depolarize the axon before the depolarizing phase of one of the oscillations crosses the threshold for impulse generation. It is not known whether this depolarizing factor is due to an intrinsic change in the afferent neuron. Once an oscillation triggers an impulse the axon fires repetitively, often for a very long time, with a very regular pattern (ie, invariant interspike intervals). The repetitive discharge is not due directly to the oscillations, but instead to an intrinsic change in the membrane, perhaps postinjury changes in the expression of ion channels. Spontaneous sinusoidal membrane oscillations have only been demonstrated in axotomized primary afferent neurons; there is no evidence that they occur in the context of primary afferent sensitization. High-frequency spontaneous discharge has been documented in patients with painful neuromas and patients with peripheral neuropathy.

However, spontaneous discharge in other neuropathic conditions may be distinctly different. For example, rats with painful peripheral neuropathy due to the chemotherapeutic drugs paclitaxel and oxaliplatin have spontaneous low-frequency (~1–2 Hz) discharge with a distinctly irregular pattern in A-fibers and C-fibers. This discharge may be due to depolarizations of the axonal membrane subsequent to an energy deficiency that is caused by a chemotherapy-induced injury to the axon’s mitochondria. It is not certain that such a low-frequency C-fiber discharge is capable of producing a sensation of pain by itself, but it is very likely that it is sufficient to produce central sensitization and hence allodynia and hyperalgesia.

**Sleeping Nociceptors**

The activation of sleeping nociceptors was first discovered as a response to inflammation, but it is now known that they have spontaneous discharge in neuropathic conditions. Microneurographic recordings from patients with diabetic painful neuropathy, small fiber neuropathies, erythromyalgia, Fabry’s disease, and other conditions have found spontaneous discharge in a large subset (10–30%) of C-fibers. This spontaneous discharge originates largely, perhaps entirely, from sleeping nociceptors. We have no information on the discharge frequency of these fibers (although there are hints that it is low frequency with an irregular pattern) and we do not know whether the spontaneous discharge is linked with the appearance of mechanosensitivity. Importantly, we do not have evidence as to whether or not discharge from activated sleeping nociceptors gives rise to a sensation of pain directly (it might not, but still might generate allodynia and hyperalgesia).

**Primary Afferent Sensitization**

There is exceedingly little evidence as to whether primary afferent nociceptors are sensitized in neuropathic conditions in either human or animal, and no evidence that such sensitization is the basis of spontaneous discharge.
In rat and mouse models of chemotherapy-evoked painful peripheral neuropathy, there is evidence for sensitization of the transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid (TRPV) channels. These channels are expressed by nociceptors, and one would predict that the channel sensitization would result in sensitization at the neuronal level. However, primary afferent sensitization has not been found in studies of C-nociceptors in rats with painful neuropathies due to anti-cancer chemotherapeutics. Instead, these animals have a subset of C-nociceptors that have an abnormally prolonged discharge of unusual pattern in response to a prolonged noxious mechanical stimulus.  

**Bystander Discharge**

In animals with partial nerve injuries, some intact C-fibers that travel in the damaged nerve have spontaneous discharge of very low-frequency (~0.2 Hz; ie, 1 nerve impulse every 5 seconds) and irregular pattern. The cause of this bystander discharge is unknown. It may be related to an inflammatory response to cellular debris generated by the nearby axonal degeneration. Whether such low-frequency discharge can result in pain or in the generation of central sensitization is unknown.

**Deafferentation-Induced Spontaneous Discharge in CNS Neurons**

Uniquely, neuropathic pain occurs in the context of nerve injury that may be accompanied by the death of the primary afferent neuron’s cell body and thus the degeneration of the spinal terminal arbor. This will deafferent spinal cord dorsal horn neurons, and deafferented neurons may develop spontaneous discharge. Spontaneous discharge in deafferented dorsal horn neurons has been documented in a man with a cauda equina lesion. Shingles is known to kill dorsal root ganglion neurons and cause the degeneration of their intraspinal terminal arbors. Thus, postherpetic neuralgia patients have deafferented dorsal horn neurons and may have spontaneous discharge of central origin.

Interruption of a peripheral nerve axon that does not cause the death of the afferent’s cell body may nevertheless result in a functional deafferentation of spinal cord dorsal horn neurons. For example, it has been shown that interruption of input from cooling-specific A-delta afferents yields a paradoxical burning pain when C-nociceptors are excited by cold. This could be thought of as the functional deafferentation of a circuit mediating inhibition of C-nociceptor input by A-delta cooling afferent input. In any case, there are no demonstrations that this phenomenon is associated with spontaneous discharge.

**The Relation Between Nociceptor Discharge and Pain**

There is no reason to doubt that intense inflammatory ongoing discharge in nociceptors will give rise to ongoing pain and will also generate and maintain central sensitization, and thereby generate and maintain allodynia and hyperalgesia. It is a commonplace observation that many acute inflammatory conditions begin with a period when ongoing pain, allodynia, and hyperalgesia are present together, and that this is followed by a period when there is no ongoing pain but allodynia and hyperalgesia persist. For example, a day after a tonsilectomy, the patient tells us that “it only hurts when I swallow.” The transition between ongoing pain plus allodynia and hyperalgesia to allodynia and hyperalgesia alone appears to be a function of discharge frequency, the number of nociceptors discharging, or perhaps to a combination of these factors.

The frequency of ongoing discharge in nociceptors in inflammatory conditions appears to be high for the first day or 2 after onset but quite low thereafter. For example, in rats with hind paw inflammation evoked by an injection of complete Freund’s adjuvant, at 7 days postinjection (when allodynia and hyperalgesia are prominent), the frequency of the ongoing C-fiber discharge is at most 1.0 Hz. It is not clear whether this low-frequency ongoing discharge is sufficient to produce ongoing pain, although it might if it were present in a large enough number of nociceptors. However, there is no reason to doubt that it is sufficient to initiate and maintain central sensitization. Experimental studies in normal human subjects have very clearly demonstrated that a stimulus that evokes a low level of C-nociceptor discharge that does not cause pain by itself will nevertheless evoke central sensitization provided that the discharge is maintained for a few tens of minutes or so.

Similarly, there is no reason to doubt that intense neuropathic spontaneous discharge will give rise to spontaneous pain, central sensitization, allodynia, and hyperalgesia. Logic and experimental data from animals indicate the possibility that spontaneous discharge of low frequency may be too weak to cause spontaneous pain by itself but nevertheless be sufficient to initiate and maintain allodynia and hyperalgesia via central sensitization.

The foregoing suggests the possibility that at least some inflammatory pain patients and at least some neuropathic pain patients may not have ongoing pain or spontaneous pain, but nevertheless have allodynia and hyperalgesia. The consequences of this are discussed below.

**Repeated Episodes of Stimulus-Evoked Allodynic and Hyperalgesic Pains in Inflammatory and Neuropathic Pain Conditions**

I suggest that what we call neuropathic spontaneous pain and inflammatory ongoing pain may in fact be partly, or in some cases entirely, due to a different phenomenon: pain due to unrecognized allodynic and hyperalgesic responses to the external and internal stimuli associated with the activities of daily life. It is of great importance to realize that in the presence of allodynia
and hyperalgesia, the activities of daily life may generate a very large number of pain episodes per day. Importantly, repeated episodes of pain evoked by the activities of daily living are likely to be especially important for the maintenance of central sensitization. Once it is established, central sensitization can be enhanced and prolonged by stimuli that are too weak to initiate it. The activities of daily life surely generate many such stimuli.

**Repeated Episodes of Stimulus-Evoked Pain in Inflammatory Conditions**

Several inflammatory conditions are associated with pain that is said to be throbbing. This is literally true—the pain stimulus is a throb, ie, the pulse; indeed, throbbing pain is often said to be pulsating pain. Throbbing pain occurs when there is edema within an enclosed anatomical compartment (eg, the pulp chamber for a tooth-ache, the joint capsule for a gouty toe) where the pulse causes an increase in compartmental pressure that activates sensitized nociceptors. Throbbing pain also occurs in vascular conditions (eg, arteritis and aneurysms) in which there is no anatomical compartment. In these cases, the pulse stretches the wall of a blood vessel that is inflamed and already stretched.

With a heart rate of 72 beats/min, there are 103,680 potentially painful throbs per day. If only one in a thousand pulsations evokes pain, then the patient will have over 100 painful events per day. It may be many more. The frequency of throbbing pain during a migraine headache was measured in 20 migraineurs and averaged 62/min, which was only a little less than the concurrent average heart rate of 80 beats/min. If the average patient’s headache lasted for only 1 hour, he would have had a total of 3,720 stimulus-evoked pains. It is more than likely that this contributes to the long-lasting craniofacial allodynia and hyperalgesia that migraineurs have after a headache.

The OA patient generally does not have pain upon awakening; instead, the joints are said to feel stiff or full. Pain begins when the joints are used in daily activities. A survey of 500 OA patients found that 89% reported use-related pain, while only 44% reported pain at rest. For OA in the hand, a conservative estimate would be that the patient flexes his fingers several hundreds of times per day, because almost every use of the hand involves finger flexion. For OA in the knee, the joint is stimulated with every step and every time the patient sits or stands; this is likely to occur at least several hundreds of times per day.

Chronic low-back pain is a particularly instructive example of the impact of everyday stimuli. I am not aware of any report that chronicles the daily pain experiences of low-back pain patients and so I will refer to my own case. I have a unilateral injury to the L4-L5 facet joint. Most of the time, I have no ongoing pain, but stimulus-evoked pain occurs about a dozen times per day. Painful L4-L5 facet joint movements occur when I sit down or stand up, twist my torso, bend sideways at the waist, or lift 1 hip higher than the other. When the injury site has been aggravated (a long plane trip does it every time) and I forego taking analgesics, I have 1 to 2 days of continuous aching pain of fluctuating intensity. Pains from the movements described above occur more frequently and are of greater than usual intensity and duration, and I now feel a stabbing pain in my back when my ipsilateral heel strikes the ground. Even a sneeze evokes a stabbing pain in the back. Like so many others with low-back pain, I try to avoid these stimulus-evoked pains by bending slightly forward at the waist (thus opening the joint space) and by trying to immobilize the joint by moving en bloc. Nevertheless, I will experience movement-related pain several dozens of times per day.

A sometimes underappreciated aspect of low-back pain is that it is impossible to avoid an important stimulus of everyday life—gravity. Gravity is the reason why so many low-back patients experience pain with prolonged sitting or standing. When the vertebral column is in the vertical position, the weight of the body compresses the facet joint. This will produce pain if the innervation of the joint is sensitized. This is stimulus-evoked pain, and the stimulus is mechanical pressure. Similar reasoning applies to discogenic and radiculopathic low-back pain (and also neck pain).

**Repeated Episodes of Stimulus-Evoked Pain in Neuropathic Conditions**

Walking is an activity of daily life. Patients with diabetic painful neuropathy (DPN) tell us that they have pain in the soles of the feet and that it feels like they are “walking on stones.” “It feels like I am walking on stones” is the pain that is caused by walking! It is stimulus-evoked pain. van Sloten et al measured activity levels via pedometer records and showed that diabetic patients with neuropathy walk significantly less than diabetic patients without neuropathy. Nevertheless, the neuropathy patients still took about 4,550 strides per day. A stride is 2 successive footfalls and the DPN patient has pain in both feet; thus, the number of potentially painful footfalls per day is twice the number of strides: 9,100. If only 1 in 100 footfalls produced pain, the patient would have about 90 stimulus-evoked pain events during the waking hours. A survey of DPN patients found that 30% reported that their pain was intermittent throughout the day. Were they reporting that it only hurt when they walked?

Breathing is an activity of daily life. Breathing involves expansion of the ribcage and this stretches the overlying skin. The thoracic postherpetic neuralgia (PHN) patient reports pain when the skin is stretched. Given a respiration rate of 12 per minute, the skin over the ribcage is stretched 17,280 times per day. If only 1 of every 100 inhalations produced stretching beyond the allodynic pain threshold, the PHN patient would have about 170 breathing-evoked pain episodes per day. I have encountered 2 patients with thoracic PHN who had learned to avoid these skin movements by panting (ie, breathing with the diaphragm only).

Getting dressed is an activity of daily life. Clothing stimulates the skin. The ability of contact with clothing
to evoke pain is very well known for patients with CRPS and PHN. For patients with thoracic PHN, pain from stimulation by clothing may be so severe that “... the victims sit stripped to the waist in the privacy of their own homes.” Thirty-eight percent of women with vestibulodynia (a common form of vulvodynia) report pain due to friction from clothing.

Speaking and eating are activities of daily life. Typically, patients with burning mouth syndrome (glossodynia) have little or no pain on awakening and a gradually increasing pain severity throughout the day. Burning mouth syndrome patients have hyperalgesia and allodynia in the tongue and perioral regions—regions that are stimulated by the movements associated with speaking, swallowing, drinking, and eating. Stimulation associated with these activities surely happens hundreds of times per day.

Fibromyalgia patients have pain evoked by normally innocuous mechanical stimuli, and these allodynic responses are accompanied by lingering pain that summates with repeated stimulation. There is a significant correlation between the patients’ ratings of their daily pain and the magnitude and duration of their allodynic pain episodes. This would be expected if the daily pain was a product of pain summation. Significant correlations between daily pain and the severity of mechanonallodynia due to activation of A-beta low-threshold mechanoreceptors (AβLTMs) have also been noted in CRPS patients. The patient with AβLTM-dependent mechanonallodynia may have burning pain every time the skin is touched; summated pain is likely to be especially prominent in such patients.

Summation of the Allodynic and Hyperalgesic Pains Due to the Stimuli of Daily Life

If we consider only the waking hours of the day (16 hours) and stimulus-evoked pain episodes that occur 100 times during the waking day, then on average such a patient would experience a pain episode about once every 10 minutes. It seems very likely that these episodes of pain will summate to produce a fluctuating level of daily pain.

Many of us have heard patients say that their pain is slight or absent upon awakening, intensifies during the day, peaks in the evening, and interferes with their ability to fall asleep. This pattern of daily pain intensity is consistent with the temporal summation of repeated stimulus-evoked pain. Many of us have also heard patients complain that their pain level is especially severe today because they “tried to do too much yesterday.” This suggests that the intensity and duration of summated pain increases as the amount of daily activity increases. The level of summated pain would be expected to fluctuate because of the interaction between the frequency of stimulus-evoked pain episodes, their intensity, and their duration. Thus, the pattern of daily pain might be continuous or intermittent, and its intensity might be constant or it might wax and wane.

It is possible that in many cases it is summated pain that the patient is referring to when asked to rate his pain. This is likely to be a common scenario: the pain patient dresses, walks to the car, sits through the trip, and walks through the parking lot and the hospital. After a time in the waiting room (on a hard plastic chair), the patient finally sits before the investigator who asks, “What is the intensity of your pain now?” This value will be recorded as the patient’s level of spontaneous, ongoing, background, overall, or usual pain. Neither the patient nor the investigator is likely to consider the possibility that this is a rating of summated pain from the many antecedent stimulus-evoked pains that are caused by a trip to the clinic. Large variation in the patients’ daily ratings of baseline pain are a significant problem in analgesic drug trials. One wonders how much of this is the result of variation in the amount of summated stimulus-evoked pain (eg, ratings obtained in the morning versus afternoon, weekend versus weekday, resting at home versus after a trip to the clinic).

There is evidence that chronic pain patients may be especially prone to pain summation. In the normal condition, there are multiple neural systems that modulate the intensity, duration, and summation of stimulus-evoked pain. Some of these systems decrease pain and some enhance it. In at least some chronic neuropathic and inflammatory pain patients, there are deficits in the systems that decrease pain (eg, diffuse noxious inhibitory controls, offset analgesia) and exacerbations of the systems that enhance it (eg, wind-up, central sensitization) (for reviews see). One might think that the duration of an episode of stimulus-evoked pain was a simple property of the stimulus’s intensity and duration. But this is not so. The duration of the pain evoked by a stimulus is governed by pain-inhibiting systems. Neuropathic pain patients may have an abnormality in these systems that results in stimulus-evoked pains of abnormal duration. Repeated episodes of stimulus-evoked pain are more likely to summate if each episode is of prolonged duration.

Coexistence of Summated Pain With Inflammatory Ongoing Pain and Neuropathic Spontaneous Pain

Summated pain may be present in cases in which inflammatory ongoing discharge is intense enough to cause pain on its own, or when neuropathic spontaneous discharge is intense enough to cause pain on its own. In such cases the patient with inflammation will have summated pain in addition to ongoing pain, and the neuropathic patient will have summated pain in addition to spontaneous pain. When inflammatory ongoing discharge or neuropathic spontaneous discharge is too weak to produce pain on its own, summated pain may be the only cause of the patient’s daily pain level.

How many patients have inflammatory ongoing discharge or neuropathic spontaneous discharge that is itself subthreshold for pain, but nevertheless supports allodynia and hyperalgesia and hence summated stimulus-evoked pain? As noted above, many patients
with chronic inflammatory pain conditions (OA, low-back pain) may be pain free in the absence of stimulation. For neuropathic conditions, it is well known that patients with idiopathic trigeminal neuralgia (tic doux-lourex) do not have pain all of the time. They have repeated episodes of paroxysmal pain separated by pain-free intervals. The pain paroxysms can be triggered by very subtle stimuli, eg, skin movements secondary to activity of the muscles of mastication, of speech, and of facial expression, and the paroxysms are sometimes followed by a period of dull, lingering pain described as “soreness.” Dubner et al have described a patient whose pain paroxysms were evoked by the slightest movement of a single hair in the eyebrow. However, idiopathic trigeminal neuralgia is in many respects a unique condition and it may have relatively little relevance to other painful peripheral neuropathies.

It has been shown that there is a large subset of women with vestibulodynia who have no pain in the absence of stimulation (provoked vestibulodynia). These patients only have pain when touch or pressure is applied to the vestibule and they thus experience pain only with tight clothing, bicycle riding, tampon insertion, intercourse, gynecologic exam, etc.

I am not aware of any detailed study of this question in DPN or PHN patients. How many DPN and PHN patients report pain-free intervals? What would happen with DPN patients if they were kept in bed all day, with their shoes and socks off, and their feet isolated from all contact? Would the feet still burn? Would there be a change in the intensity or quality of the daily pain? It would be difficult to prevent incidental skin stimulation in a patient with thoracic PHN (he has to breathe), and the trigeminal PHN patient would be a poor choice for study because the face is so mobile, but PHN also occurs in an arm or a leg. Do patients with arm or leg PHN have pain when incidental stimulation is carefully excluded for a day?

Conclusions

It is suggested that the following definitions will aid our thinking about pain mechanisms: 1) Ongoing pain (pain due to inflammatory ongoing discharge caused by the ongoing presence of the products of inflammation; 2) spontaneous pain (pain due to neuropathic spontaneous discharge in somatosensory neurons that is caused by changes that are intrinsic to the neuron; and 3) summated pain (pain due to the temporal summation of alldynie and hyperalgesic pain episodes that are evoked by the stimuli of daily life [in either inflammatory or neuropathic conditions]).

For neuropathic pain, we need detailed chronicles of the temporal characteristics of the patient’s daily pain experience. We need to explore the possibility that some patients may suffer largely from summated stimulus-evoked pains rather than spontaneous pain. Experimentally, we need more information about the status of the mechanisms that regulate the duration of stimulus-evoked pain in humans and animals with inflammatory and neuropathic pain conditions.

It has been said that our search for new analgesics for the control of neuropathic pain is faltering because we are measuring the wrong thing in the animal. The preceding discussion suggests that the problem may be the reverse—we may be measuring the wrong thing in the patient. In clinical trials, the statistically incapacitating variability that we see in the patients’ reports of “daily,” “usual,” or “average” pain may be the result of an imprecise question. It is possible that most patients do not have a single pain, but rather different kinds of pains, and that stimulus-evoked pains (both summated and nonsummated) are prominent parts of their complaint. It would be expensive to measure stimulus-evoked pains and the daily course of summated pain in the context of a clinical trial. But not as expensive as a trial that fails because of an imprecise end point.

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