Causalgia and Denervation Supersensitivity

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Abstract: There are many explanations for causalgia but none entirely satisfactory. This paper postulates that the many manifestations of causalgia may be explained by the phenomenon of "denervation supersensitivity." Typically, causalgic pain appears about a week following a nerve injury when supersensitivity has had time to develop, leading to increased muscle fiber and neuron sensitivity to transmitter substances; spontaneous electrical activity and an ability to receive synaptic contacts from various sources, including autonomous fibers. At synapses, pre-synaptic inhibition is attenuated with facilitation of noxious input at the dorsal horn and heightened interneuronal activity. The severe, burning pain may be explained by hypersensitivity of nociceptors and small-diameter afferent fibers. Autonomic dysfunction and trophic changes may follow supersensitivity of receptors around blood vessels and spontaneous activity at autonomic ganglia. Since denervation supersensitivity is reduced by electrical stimulation, this may be a possible modality for pain relief.

THE TERM "causalgia"[1-12] is derived from the Greek "kausis" (burning) and "algos" (pain) to describe the most striking feature of the condition which is persistent, severe and burning (though not always) pain in an affected extremity, usually as the result of a partial injury to a nerve (commonly to median and tibial nerves). In addition to the pain of variable intensity (and therefore a wide variety of names—see Table 1), there is autonomic dysfunction and trophic changes in skin and/or bones in the involved parts. Exacerbated by certain stimuli and capable of temporary or nearly complete alleviation following sympathetic blocks, causalgic pain has been categorized as "major causalgia" and a less painful variant referred to as "minor causalgia" or "post-traumatic reflex sympathetic dystrophy." Typically, causalgic pain appears about a week following a nerve injury, reaches its height in four to five months and tends to disappear slowly, many persisting for up to two years. Its incidence has been estimated to vary in frequency from 1.8 to 12 percent of nerve injuries. Although the clinical features are well known, its exact pathogenesis remains unknown.

The burning pain was first described by Denmark in 1813 and the glossy skin by Paget in 1864 and in the same year appeared the classic treatise on "Gunshot wounds and other injuries of nerves" by Mitchell, Morehouse and Keen.[1] Mitchell subsequently applied the term "causalgia" to the condition.

Mechanism of Pain

Many explanations have been advanced to account for the development of causalgia but none is entirely satisfactory. Two of these are frequently quoted. Doupe[3] had advanced the

Presented at the Second World Congress on Pain, Montreal, Canada, August 27-September 1, 1978.

theory that trauma may cause the formation of artificial synapses (ephapses) between sympathetic efferents and somatic sensory afferent nerves. According to this theory, a sympathetic impulse travelling down the efferent nerve, in addition to its usual effects, causes a depolarization of the somatic sensory nerve at the point of artificial synapse. This depolarization is then propagated orthodromically along the afferent sensory nerve and when added to normal sensory impulses causes abnormally high sensory discharge which is felt as pain. In addition, depolarization at the artificial synapse is said to propagate antidromically along the somatic afferent leading to the release of certain algogenic substances which decrease the threshold at the sensory nerve ending and further increase the impulses reaching central areas. Experimental confirmation that fiber interaction can occur between injured nerves supports the theory of Doupe but does not explain all of the manifestations of causalgia. For example, sometimes local anesthetic blockage distal to a nerve lesion can cause relief of the pain with the period of pain relief often outlasting the duration of the block. However, electrical stimulation of the distal end of the divided peripheral nerve can cause pain by releasing algogenic and vasodilator substances which when collected and injected into the skin elsewhere can cause burning pain.[13]

Livingston[14] postulated his theory of the "vicious cycle of reflexes" in which there is said to be chronic irritation of a peripheral sensory nerve leading to increased afferent impulses and resulting in abnormal activity in an "internuncial pool" of neurons in the spinal cord.

More recently, the "gate control theory" of Melzack and Wall[15] has been applied to causalgia, but although the concept of a "gate" is still valid, mere altered ratio between large and small fibers is now known to have little or no bearing on pain.[16] Thus, there are pro's and con's for all these theories but none are entirely acceptable. This paper postulates that the many manifestations of causalgia may be explained by the phenomenon of "denervation supersensitivity."

Cannon and Rosenblueth's law of denervation[17] stated that "when in a series of efferent neurons a unit is destroyed, an increased irritability to chemical agents develops in the isolated structure or structures, the effects being maximal in the part directly denervated." They showed that denervated striated muscle, smooth muscle, salivary glands, sudorific glands, autonomic ganglion cells, spinal neurons and even neurons within the cortex develop supersensitivity. Today, repeated animal experiments have confirmed that denervation supersensitivity is indeed a general phenomenon and that actual physical interruption is not necessary for denervation supersensitivity to develop.[18-24] Minor degrees of damage or even experimental exposure of motor axons to poisons such as colchicine or vinblastin can destroy the microtubules within the axons. Such a nerve still conducts nerve impulses, synthesizes and releases transmitter substances and evokes muscle contractions, but the muscle cells innervated by the affected axon becomes supersensitive as if the muscle had been denervated.

The changes following denervation supersensitivity are probably present in all target cells, but those in muscle and nerve have been extensively studied. In muscle and nerve, it has now been shown that there is an increase in the surface area of the muscle fiber or neuron that is sensitive to acetylcholine. Normally, the area of receptor sensitivity in muscle is sharply circumscribed to the end-plate region, and in the neuron, it occurs only at the synapse; but in denervation supersensitivity there is a marked increase in the degree to which extrajunctional membrane responds to the application of acetylcholine. This change is detectable within a matter of hours and reaches a maximum in about a week, by which time the entire surface of the muscle fiber or neuron is as sensitive to acetylcholine as the normal end-plate region or synapse. This development of supersensitivity probably represents incorporation of newly-synthetized receptors into extrajunctional membrane.

A second important change is the onset of spontaneous electrical activity of fibrillation. Normally, a muscle gives an action potential only in response to the release of the transmitter agent. In contrast, action potentials begin to occur spontaneously within a few days of denervation and continue for as long as the muscle remains denervated, in some cases up to a year or more. This autogenic activity, now known to arise also in neurons (especially in denervated sympathetic nerves), probably results from local fluctuations in membrane potential and the increase in membrane conduction to electrolytes. Other changes include those in cell structure and biochemistry and atrophy eventually follows. Another important but little understood change in denervated muscle fibers and neurons is a renewed ability to receive synaptic contacts. Normally, these cells resist foreign innervation but in denervation supersensitivity they accept contacts from a wide variety of sources, including other motor nerves, pre-ganglionic autonomic fibers and possibly even sensory nerves. Both denervated muscle fibers and neurons induce sprouting of nearby pre-synaptic elements; denervated autonomic neurons, in particular, are prone to receive a variety of foreign synapses.

Changes at synapses also occur. The studies of Hughes, Kosterlitz[25-30] and others have shown that endogenous morphine-like peptides (endorphins and enkephalins) inhibit neuronal activity by altering sodium conductance at opiate receptors in the brain and at the spinal cord levels. Methionine-enkephalin is a neurotransmitter found in spinal grey matter, occurring at the terminals of interneurons. Excitation of these interneurons, which interact with one another and impinge on the nerve endings of sensory nerves, produces primary afferent depolarization or pre-synaptic inhibition and attenuates nociceptive transmission across the synapses of primary afferent fibers and second-order neurons, especially in Laminae I, II and III. Chronic lesion of primary afferents may decrease the number of opiate receptors in interneuron terminals at the dorsal horn with a corresponding reduction of interneuronal activity and pre-synaptic inhibition by enkephalin. Peripheral nerve disease may thus also cause facilitation of noxious inputs at the dorsal horn and heightened impulse traffic at autonomic ganglia where interneurons have also been described. Since supersensitivity occurs as a general phenomenon following denervation, heightened neuronal and interneuronal activity may exist throughout the nervous systems — peripheral, central and autonomic.

Discussion

Typically, causalgic pain appears about a week following a nerve injury when denervation supersensitivity has had time to develop. In addition to direct physical trauma, a nerve may be compressed by haematomata.[31] Even though a peripheral nerve may have an extensive plexus of blood vessels, occlusion of a few major feeding vessels or of many smaller *vasa nervorum* can cause neuropathy.

The severe, burning pain in causalgia may be explained by hypersensitivity of nociceptors and small-diameter afferent fibers (A-delta and C) in cutaneous and other tissues. The autonomic dysfunction and trophic changes may be the result of autogenic fibrillations in sympathetic neurons and increased activity at autonomic ganglia, thus, a sympathetic nerve block and/or sympathectomy may provide relief in a proportion of patients. (Both the median and tibial nerves are rich in autonomic fibers).

Doupe's suggestion that trauma causes the formation of "artificial synapses" (ephapses) between sympathetic efferents and somatic sensory afferent nerves may occur in denervation supersensitivity with the renewed ability of neurons to receive synaptic contacts and the formation of abnormal synapses.

Livingston's theory of a "vicious cycle of reflexes" and hyperirritability of a peripheral sensory nerve with increased afferent impulses and abnormal activity in an "internuncial pool" of neurons in the spinal cord may also be explained by the phenomenon of denervation supersensitivity since peripheral receptors, afferent neurons, internuncial pools and

Table 1.
Wide variety of names and severity.

Causalgia — major and minor.
Post-traumatic reflex sympathetic dystrophy.
Reflex hyperemic deossification (De Lorimer).
Sudeck's atrophy.
Traumatic reflex osteodystrophy.
Reflex trophoneurosis.
Acute bone atrophy (De Takats).
Reflex nervous dystrophy.
Post-traumatic painful osteoporosis (Leriche).

autononomic ganglia may all become hypersensitive or hyperreactive.

Today, a gate-controlled system is still held to be a valid[16] (though altered remaining fiber spectrum is no longer correlated to pain). However, facilitation of noxious input may occur at the dorsal horn from a loss of presynaptic inhibition.

A peripheral nerve injury may produce dysfunction which may be motor, sensory, trophic or autonomic[32-34] but these components may occur in variable amounts and to varying degrees. When changes are minor, they are often missed clinically, especially when few pain fibers are affected. The difference between major and minor causalgia is probably one of degree, paralleling involvement of the pain and autonomic components.

Implications for Treatment

Lomo[35] in animal experiments has shown that denervation supersensitivity is reduced or abolished by electrical stimulation. He demonstrated that hypersensitivity, as assayed by the sensitivity of muscle extrajunctional membrane to acetylcholine, diminished at a rate which depended critically on the amount and pattern of the stimuli. The rate of decline of acetylcholine hypersensitivity was enhanced in an apparently continuously graded manner with increase in the number of stimuli, or if the number of stimuli was kept constant, with the stimulus frequency within the train. High frequency stimulation was found to be more effective, e.g., 100 hertz was found to be ten times more effective than 10 hertz. High frequency stimulation was also more effective in delaying the appearance of hypersensitivity when stimulation was stopped. Even very low levels of stimulation strongly suppressed hypersensitivity. In the past year, four patients with symptoms of minor causalgia and one with those of major causalgia were treated with transcutaneous neural stimulation with good results. Although treatment by stimulation of the peripheral nerve has been previously reported,[36] it was on the hypothetical basis of pain suppression by selective large-fiber stimulation rather than by attenuation or ablation of denervation supersensitivity.[37]

The natural history of the affliction and its tendency to gradual but spontaneous resolution would seem to correspond to the slow rate of nerve regeneration[38] with some persisting for many months.

Conclusions

Many explanations have been put forward to account for the symptoms of causalgia but so far none is entirely satisfactory. This paper postulates that its many manifestations may be explained by the phenomenon of denervation supersensitivity.

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