Why Standard Pain Management Needs to be Modified for Elderly People

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Abstract

Data from clinical studies suggest that there is an overall decrease in pain sensitivity with advancing age. Evidence indicates that aging is associated with the degeneration of nociceptive pathways. Specifically, primary afferent fibers undergo degenerative changes including decreased trophic support and decreased expression of several ion channels. Significantly, aged primary afferents (in humans or experimental animals) show axonal involution, Wallerian degeneration and decreased neurotransmitter content, which are alterations that represent a defective pain transmission in elderly people. These observations suggest that clinicians must predict a greater level of underlying pathology when elderly persons make a report of pain and that the standard pain management needs to be modified to meet the special needs of elderly people.

The elderly population is growing

Because life expectancy continues to rise, a major shift in the age distribution of the world's population is expected. In 2003, nearly 36 million people age 65 and over (elderly) lived in the United States, accounting for just over 12 percent of the total population[1]. Worldwide, the elderly population is growing by an unprecedented 800,000 persons/month, according to a report issued by the U.S. Census Bureau and the National Institute on Aging[2].

Pain as an early warning system

In the absence of disease, pain is a key mechanism utilized by the body to warn of impending tissue damage. Compromises or failures of this warning system can have catastrophic effects, as seen in patients with leprosy and diabetes. Children with congenital insensitivity to pain (recently shown to be a genetic disorder) experience accidents and injuries more frequently and die of infection at an early age. Patients with diabetic neuropathy provide another example of the value of pain. These patients often lose the sense of touch, pain and temperature in their lower extremities due to polyneuropathy and are subject to severe infections and wounding. Unrecognized burns, puncture wounds, and bone fractures are common in such individuals. Thus, normal pain perception plays a crucial role in the survival of an organism.

Pain sensitivity in aging

This early warning system appears to be altered in elderly persons since, as a group, they show an increased pain threshold (or decreased pain sensitivity) in the absence of any disease. Pain threshold is defined as the lowest stimulus value at which the person reports pain. The quantitative sensory testing to measure pain thresholds, therefore, offers an approach for evaluation of functional integrity of the entire neural pathway. The measurement of pain threshold and suprathreshold sensitivity in healthy volunteers of various ages has been performed in over 40 separate research studies to date (for review, see [3]). These studies have employed controlled electrical, mechanical and noxious heat stimulation applied to different sites on the body, including the hand, forearm, forehead and sole of the foot. Although there were marked technical and methodologic differences between the various studies, and the mean age of the

study population varied considerably, with remarkably few exceptions, these studies consistently demonstrated a mild to moderate decrease in mechanical and thermal pain sensitivity with advancing age[4,5]. Thus, despite marked differences in study design and outcome measures, a mild to moderate decline in pain sensitivity is consistently observed in elderly subjects.

Degeneration of peripheral receptors and nerve fibers

Morphologic studies of the peripheral nervous system have shown that aged primary afferent nociceptors undergo several degenerative changes during aging, including the loss of both myelinated and unmyelinated nerve fibers. Early studies in this area assessed cutaneous nerve fiber integrity in normal adult and aged individuals, using silver stains to quantify Meissner corpuscles, a mechanical receptor present in glabrous skin of the palm, foot and toe[6]. These studies revealed a steep, age-related decline in the density of Meissner corpuscles.

In addition, electron microscopic studies of human sural nerve have shown marked degeneration of myelinated fibers in aged tissue. The ultrastructural changes observed in this study included segmental demyelination and Wallerian degeneration, which were very frequent in the elderly subjects compared to subjects under 35 years of age[7]. Similarly, in peripheral nerves of several animal species, a reduction in the number or density of both myelinated and unmyelinated fibers due to aging has been reported[8]. Another study investigated the myelinated and unmyelinated axon populations in dental pulp[9]. A total of 2,684 nerve fibers were measured in 16 subjects aged 10 to 72 years. The pulps from aged patients showed a loss of A-delta fibers and a decrease in the number of unmyelinated fibers relative to pulps from younger subjects. In fact, a progressive decline was reported, such that the more elderly the patient, the greater the average reduction in C-fiber diameter. As described above, these fibers are critical for transmitting pain sensations. The quantitative morphologic parameters of the myelinated nerve fibers were similarly affected, with a decrease in size, circularity and myelin thickness in the aged animals. Interestingly, a reduction in the synthesis of myelin protein mRNA expression with aging is thought to contribute to the above changes in the myelinated fibers[10, 11]. In addition, the decrease in axonal size reported in the study above may be due to a reduction in neurofilament complement since these organelles are an important component of the cytoskeletal framework and the major determinants of axonal caliber. This possibility is strengthened by the observation that the rate of axonal transport of various materials is reduced with increasing age[12]. Conceivably, a reduction in neurofilament composition within the sensory axons could lead to decreased axonal size, and ultimately to axonal degeneration.

Neurochemical changes in peripheral nerve

Substance P (SP) and calcitonin gene-related peptides (CGRP) are released from primary afferent nociceptive fibers upon painful stimulation or pathological states. They produce neurogenic inflammation, a major part of a normal inflammatory response in tissue. Antidromic electrical stimulation in the nerve trunk causes vasodilatation, which is explained by release of SP and CGRP from nerve endings. Studies that measured SP and CGRP content in the peripheral nerve cell body (dorsal root ganglia) and peripheral nerve showed a reduction in their levels with increased age. Radioimmunoassay has shown that SP levels were significantly reduced in the cell body and in the sciatic nerve of old rats (57.9 ±13.6 and 21.4 ±10.7 fmol/mg) compared to young rats (82.9 ±19.2

and 57.5 ± 20.8 fmol/mg)[13]. Since these are major neurotransmitters of primary afferent neurons, a reduction of their level suggests decreased density or functional integrity of nociceptive afferent fibers.

Altered expression of transduction channels in neurons

Peripheral receptors in the primary afferent fibers must convert painful stimuli into electrical signals for transmission to the spinal cord. Recently, a transducer for noxious heat stimuli has been discovered. TrpV1 is a receptor for the pungent ingredient in pepper, capsaicin. TrpV1 is also a heat-transducing protein capable of responding to moderate (43 to 48°C) heat [14]. This temperature corresponds to the heat pain threshold in humans. Immunolabeling shows an apparent reduction in the number of TrpV1 positive fibers in tibial and saphenous nerves of aged animals when compared with six-week-old animals. A general decrease in TrpV1-positive fibers was also apparent when comparing the overall number of TrpV1-positive fibers coursing through the nerve bundles in the deep dermal tissue of the foot. Such a reduction of TrpV1 channel proteins in the DRG cell bodies and afferents could alter the heat threshold of firing.

Compared to heat stimuli, less is known about the molecular mechanisms of mechanical stimuli like touch, pressure and noxious pinch[15]. However, the afferent sensitivity is highly dependent on the expression of several classes of membrane channel proteins that regulate ion flow in response to a given stimulus. Sodium channels are involved in the generation and transmission of impulse trains in response to mechanical[15] and thermal[16] stimuli. Functional studies reveal that sodium channel subtype Nav1.8 and Nav1.9 have a specialized role in mediating pain. Very recently, one study showed that Nav1.8 channel expression is decreased in aged rats[17]. The segmental demyelination of peripheral nerve due to aging, observed in some studies, may also result in reorganization of voltage-sensitive sodium channels in the axonal membrane[18]. Thus, the alteration in gene expression and/or distribution of these transduction channels in aging neurons may lower their sensitivity to natural stimuli.

Decreased trophic support: a possible mechanism for age-related neuronal changes

Growth factors are known as a survival factor for embryonic neurons, but they can also affect pain transmission in the adults. Nerve growth factor remains the best known example of a fully characterized trophic agent, which is produced from non-neuronal cells and binds to its receptors located on primary afferents and then is retrogradely transported to the nerve cell body[19]. Nerve growth factor produces localized pain and tenderness when injected intradermally in humans[20]. The parenteral administration of nerve growth factors in rodents results in profound heat and mechanical hyperalgesia [21]. NGF has been shown to upregulate neuropeptides, tetrodoxin-resistant, voltage-dependent sodium channels[22], acid sensing ion channels[23], and the capsaicin receptor TrpV1[24]. A decline of nerve growth factor receptor (TrkA and p75) expression was found in aged rats[25] and in the sympathetic nervous system of aged mice[26]. The GFRalpha3 receptor, which binds the growth factor artemin and is expressed by TrpV1-positive neurons, was also decreased in the dorsal root ganglia of aged animals. The decreased trophic support of aged primary afferents may impede the synthesis and transport of neuronal transduction channels such as NaV1.8 or TrpV1 and thereby reduce sensitivity, leading to a higher pain threshold.

Effects of aging on peripheral afferent function

It has been reported that the compression over nerves could block A-delta fiber activity[27]. The study showed that elderly individuals exhibited a stable pain threshold throughout the study, but younger patients exhibited an increase in pain threshold during superficial nerve compression (A-Delta fiber block). The authors of this study concluded that elderly people might rely upon C fibers alone, whereas younger individuals use both types of afferent fiber, and that elderly individuals have impaired A-Delta function.

Conclusion

An important conclusion of this review is that damage in the peripheral pain transmission pathway due to aging is substantial. This includes structural damage of peripheral receptors and axons, alteration of neuropeptide content and expression of the ion channels responsible for heat and mechanotrasduction. These degenerative changes in the pain pathway may, in part, be responsible for increased pain threshold in elderly people. Therefore, clinicians must predict a greater level of underlying pathology when elderly persons report pain. Moreover, if the pain transmission pathway of elderly people is defective, then standard pain management needs to be modified to meet special needs.

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