Plenary Lecture at 1st International Ryodoraku Congress

Oct. 8, 1988—Miyazaki—

Chairman Prof. M. Hyodo

Acute Pain and Chronic pain

Hideo Yamamura, M. D.

Emeritus Professor of Tokyo University

In this lecture, I would like to explain the difference between acute pain and chronic pain. There is very significant difference between acute and chronic pain. Acute pain usually arises from noxious stimuli which include pinch, heat or electric shock of significant intensity. In clinical practice, noxious stimuli include mechanical damage and chemical factors due to inflammation.

The clinical symptoms and signs of acute pain are similar to those seen in anxiety state : increased cardiac rate, increased blood pressure, pupillary dilatation, palmar sweating, hyperventilation, hypermotility and escape behaviour. Acute pain promote survival and restitution, thus serves useful biologic function to the body.

When pain persists, physical discomfort is altered by psychological factors and it becomes chronic pain. Chronic pain, by definition, persists for a long time (usually more than 6 months) . There may or may not be an identifiable underlying disease process or healing may have occurred, but pain persists.

The clinical symptoms and signs of chronic pain states are similar to those seen in depression states : sleep disturbance, irritability, appetite disturbance, constipation, psychomotor retardation, social withdrawal and abnormal illness behaviour. It is usually destructive physically, psychologically and socially. It serves no useful biologic function to the body.

Chronic pain can be divided into nociceptive related to tissue injury and non-nociceptive which include deafferentation and psychogenic pain.

Nociceptive pain is the most common type in cancer and chronic illness. However, chronic cancer pain has many of the characteristics of both chronic and acute pain. The pain represent continuous application of a noxious stimulus and continual renewal of acute pain. Yet, because of chronic distress and anxiety, it has many psychological components of chronic pain.

Deafferentation pain is due to nervous system injury that interrupts the neural transmission of sensory impulse. The most common type of deafferentation pain are brachial plexus avulsive pain, post-herpetic neuralgia, phantom limb pain and thalamic pain, syndrome.

Psychogenic pain may take the form of somatic pain without any organic pathology or pathophysiological mechanism to account for the pain.

Chronic pain is different from acute pain not only from the view point of psychological aspect but from that of mechanisms. In this respect, I will explain the difference between acute pain and deafferentation pain.

Acute pain

Acute pain is evoked by noxious stimuli that injure or threaten to destroy tissue. The receptor which produces pain by noxious stimulation is called nociceptor. They are supplied by both small myelinated A δ fibers and unmyelinated C fibers. They are definitely distinguished from non-nociceptors, because non-nociceptors can not produce pain even if noxious stimulus is applied.

There are three types of nociceptors : high-threshold mechanoreceptor, a heat nociceptor and polymodal nociceptor or polymodal receptor. Nonnociceptor is called low-threshold mechanoreceptor.

This slide shows the schema of the responses of nociceptors and non-nociceptor to the various intensity of stimulation. In this slide, horizontal axis is stimulus intensity and vertical axis the unit discharge of the neuron. High-threshold mechanoreceptor responds only to noxious range of mechanical stimuli. This does not respond to the pressure but responds to a pin prick or to a pinch.

Polymodal receptor can not only responds to noxious heat, chemical and mechanical stimuli but also responds to a non-noxious stimuli. They are not only sensitive to wide variation of stimuli but also wide range of stimulus intensity. Endogenous pain producing substances as bradykinin activates only polymodal receptors.

In the non-nociceptor , unit discharges do not further increase even if noxious stimulus is applied.

As described by Rexed, the spinal dorsal horn is divided into six laminae. Lamina I and II are superficial layers and from lamina III to VI are nucleus proprius.

In the dorsal horn, there are two categories of neurons that receive input from nociceptive afferents. The first type is called nociceptive specific neurons (NS neurons) and they respond only to intense mechanical and heat stimulus. They do not respond to non-noxious stimuli.

The second type of neurons are called wide-dynamic range neurons (WDR neurons) . They are activated by hair movement or weak mechanical forces, but fire at the highest rates when nociceptors are stimulated. NS and WDR neurons correspond to the Transmission cells in the Gate Control Theory proposed by Melzack and Wall.

Besides these neurons, there is another one in the dorsal horn. It is low-threshold mechanoreceptor neuron which fires maximally by weak mechanical stimulation.

NS neurons are concentrated in the lamina I and its adjunct outer zone. WDR neurons are found in lamina I, II and IV–VI. Low-threshold mechanoreceptor neurons are distributed from lamina II to V. Activities of these neurons can inhibit the responses of NS and WDR neurons to noxious stimuli. In other words, activity of A β fibers which comes from low-threshold cutaneous mechanoreceptor inhibits the pain caused by NS and WDR neurons. This is the mechanism of Gate Control Theory.

NS neurons send long ascending axons to the thalamus (neo-spinothalamic tract) . This system might be involved in signalling “first pain”.

WDR neurons send ascending tract as paleo-spinothalamic tract. This tract projects to medullary, mesencephalic reticular formation and limbic system. This tract might be involved in signalling “second pain” and in reflexive modulation of autonomic nervous function as well as that of fundamental body function.

Descending inhibitory system of pain

The responses of the dorsal horn neurons to noxious stimuli are controlled from various brain regions via descending pathways. Thus analgesia is obtained by electrical stimulation of brain sites. This phenomenon is called stimulation produced analgesia. This descending system may act as a “gate control system” to the dorsal horn neurons.

For instance, Liebeskind have shown that electrical stimulation of neurons in the PAG results in inhibition of the transmission of nociceptive afferent in the spinal dorsal horn in the cat. This slide is a frequency histogram of the spike discharge of nociceptive neurons in lamina V. These neurons respond vigorously to sustained or briefly applied strong pinches. These responses are inhibited during PAG stimulation.

According to Dr Yokota, PAG stimulation powerfully suppresses the responses of WDR neurons in the dorsal horn to noxious heating of the cutaneous receptive field. During concomitant PAG stimulation, the slope of the temperature-response curve is reduced.

Other studies have shown that Ncl. raphe dorsalis, Ncl. raphe magnus and Ncl. reticularis gigantocellularis of the brain stem are also the sites from which powerful pain inhibitory effect can be obtained.

This slide shows the spontaneous discharges of WDR neurons in lamina V before, 5 and 30 minutes after administration of morphine 1 mg/Kg i.v.. The spontaneous discharges are suppressed by morphine and this suppression is more pronounced in the spinal cord intact animal than the transected one as explained in the next slide.

This slide shows the effect of morphine on the evoked discharges of WDR neurons in lamina V by noxious stimuli. Evoked discharges are expressed as percentage from the control value along with time course. Solid lines are intact group and dotted line spinal transected group. You will note that in intact group, the suppression by morphine is greater and longer than in transected group. These results indicate that morphine has not only a local suppressive effect on dorsal horn neurons, but also it activates brain stem structures which in turn produce suppression via descending inhibitory pathway.

Dr. Takagi has revealed by microinjection of morphine that Ncl. reticularis paragigantocellularis and Ncl. reticularis gigantocellularis are the main sites for producing opiate analgesia. This analgesic effect is mediated by nor-adrenaline, serotonin and other neurotransmitters.

Next slide shows the summary of the pathways which mediate pain and suppress pain. Nociceptive afferent neurons exit dorsal horn neurons with axon ascending in the neospinothalamic system (yellow line) and paleospinothalamic system (blue line).

Neospinothalamic system projects to the sensory cortex through thalamic neurons. Paleospinothalamic system projects to medullary and mesencephalic reticular formation neurons which have diffuse cortical connection and project to limbic system.

Descending pain suppression pathway on the left may include paraventricular thalamus, periaqueductal gray and raphe nucleus. This system descends in the dorsolateral funiculus and suppresses the nociceptive activation of dorsal horn neurons.

Chronic pain mechanism

In the chronic pain, prolonged stimuli and prolonged response can not be simply explained

by a prolongation of acute pain mechanism. In this case, the time course and the repairing process must be considered.

Professor Wall has proposed that if event is prolonged, new factors enter the linkage between stimulus and repair.

According to Prof. Zimmermann, motor and sympathetic reflexes to noxious stimuli are usually aimed to decrease the effect of noxious stimulus.

However, in chronic pain, these reflexes increase rather than decrease the effect of noxious stimulus.

For example, a motor reflex initiated by a cutaneous pain might set up activity in muscular nociceptor by contraction of the muscle. This in turn can increase the motor reflex which will lead to self-sustained muscle spasm and to on-going pain.

Such a vicious circle is also found in the sympathetic reflex. Nociceptive afferent activates sympathetic nervous system which in turn changes microcirculation, smooth muscle tone and chemical environment.

positive feedback might be considered as causative in the syndromes of sympathetic reflex dystrophy.

When tissue is damaged the pain producing substances are released. They either stimulate the nociceptors or sensitize them to mechanical and heat stimuli. The pain producing substances might also affect the microenvironment of the nociceptor by changing smooth muscle tone, local circulation and capillary permeability. Interestingly, by the antidromic activation of the sensory nerve, a potent pain producing substance is liberated from the ending.

Sympathetic efferents are also playing a role in modifying nociceptor sensitivity by exciting and sensitizing regenerating fibers, contracting smooth muscles, changing blood flow and capillary filtration and releasing algescic substances.

Morphological changes also occur. After the injury, chemical substances like substance P is liberated from C fibers. From the damaged tissue, also chemical substances such as histamine, bradykinin, serotonin are liberated.

As a reparatory process, phagocytes and fibroblasts as well as capillaries will invade the damaged tissue. The sensory and sympathetic nerve will be regenerated here.

At this stage, it is thought that C fibers are transporting abnormal chemicals to the posterior ganglion and possibly to the C fiber terminals by an axon transport. Therefore, the C fiber afferents are suspected of being particularly important in inducing the changes of chemistry and physiology of dorsal horn. These chemical and morphological changes will change the physiological function of nociceptors.

At Peripheral axon, the morphological changes start with degeneration and proximal sprouting. Sprouts become spontaneously active and also sensitive to mechanical stimulation. They become very sensitive to the low concentration of nor-adrenaline.

Several weeks after injury, a stable electrical interaction (ephapse) is formed between sensory and motor axons. This form of crosstalk is long lasting. There is a possibility that abnormal chemicals are transported to the spinal cord by the injured nerve and sprout.

Nearest intact nerves send the sprouts to the denervated tissue and occupy this area.

In this slide a neuroma was induced by placing the proximal stump of rat sciatic nerve into

the plastic cap. This slide shows that neuroma is very sensitive to nor-adrenaline. This study was done by Dr. Wall. In this preparation, ongoing impulse activity was found in A δ and C fibers which was initiated at the fiber sprout in the neuroma.

This ongoing impulse discharge was enhanced by i. v. administration of nor-adrenaline. This effect was prevented by simultaneous injection of the alpha blocker phentolamine. This is indirect evidence that sympathetic efferents might exert some stimulating action on nociceptive fibers in the neuroma. When a short period of repetitive electrical stimulation was applied to the nerve, the ongoing discharge was completely stopped for several minutes. This is a possible foundation for analgesia produced by peripheral stimulation of amputee.

In the proximal axon to the injury, the dorsal root ganglion cells become spontaneously active. Thus the injured axon becomes to generate the abnormal discharges from two sources. One is from sprouts and the other from the dorsal root ganglion cells.

At the terminal of C fibers, peptides and chemicals are reduced remarkably after two weeks of injury. The significance of this change is not clear because the conduction of impulse is still maintained. The conduction velocity of nerve is decreased.

At later stage, atrophy of some terminals and degeneration of some dorsal root ganglion cells are observed. After 6 months of injury, depleted chemicals at C fiber terminal begin to recover.

Dorsal horn organization changes as a result of peripheral nerve injury.

The immediate effect of cutting afferent is to abolish the receptive field of cells which are normally excited by the cut afferents.

After some days, there is a collapse of the presynaptic and postsynaptic inhibitory mechanisms associated with the deafferentated cells. These changes result in a marked rise in the excitability of the cells.

For some cells, this increased excitability is sufficient for them to begin to respond to afferent which were previously inactive. The result is that the cells adopt a new receptive field activated by the nearest intact afferent.

The consequences within the dorsal horn are chronic readjustment of excitation and inhibition of pain. By this resetting of the central control of pain, pain persists after the original peripheral signal has ceased.

In summary, I have explained the difference between acute and chronic pain, especially from the view point of neural mechanism. It is important to recognize these differences because correct management of these two groups is so different. In the acute pain, all analgesic medications are indicated although attention should be directed toward identifying and treating the underlying etiology.

In the chronic pain, no cure can be anticipated from the cutting pain pathway or by the usual analgesics. For the management of chronic pain we have to understand the complexity of chronic pain mechanism and also to recognize the patient psychological change or suffering.