SYMPATHETIC MODULATION

H. Hooshmand, M.D., and Eric M. Phillips
Neurological Associates Pain Management Center
Vero Beach, FL 32960

INTRODUCTION

The sympathetic function is modulated at all levels of peripheral and central nervous system from the dorsal root ganglia (DRG), to substantia gelatinosa (SG).

At the periphery, the efferent sympathetic nerves control the circulation. The afferent sympathetic nerves are influenced by the putative effects of acetylcholine and dynorphin on one end, and the substance P (SP) on the other.

At the spinal substantia gelatinosa (SG) level of dorsal horn (DH) the superficial layers I-III receives substance P(SP) from the periphery. The deeper layers IV and V act as inhibitory layers showing high concentrations of dynorphin.

Descriptors. *complex regional pain syndrome (CRPS), dorsal horn (DH), dorsal root ganglia (DRG), inflammation, plasticity, reflex sympathetic dystrophy (RSD), substance P (SP), substantia gelatinosa (SG), wide dynamic range (WDR)*

REFLEX SYMPATHETIC DYSTROPHY(RSD)

In reflex sympathetic dystrophy (RSD), due to the prolonged input of pain, layers I-III show a gradual death of granular cells (small inhibitory cells that control the input of pain stimulus to the spinal cord). Secondarily, the concentration of dynorphin in the SG is increased. This is a plastic response to counteract the poorly inhibited pain sensory input.

With prolonged pain stimulus, arborization of afferent pain fibers in the DH occurs. This secondarily causes more excitation of the sensory input with resultant exhaustion and death of the granular inhibitory cells (1).

With the death of the granular cells there is less inhibition of pain, and at the layer V of DH the vertical spread of wid dynamic range (WDR) of Nathan and Roberts occurs (2,3). The stimulus spreads to adjacent levels of the spinal cord with further stimulation of sensory input. This is the beginning of the spread of sympathetic dysfunction. The WDR nerve cells are polymodal and may be activated by a wide range of stimuli.

The prolonged input of pain sensation in the form of dermal vasoconstriction due to inactivity or application of ice through A-beta mechanoreceptors (responsible for allodynia), result in a constant bombardment of the DH granular cells and further death and destruction of these cells at layers I-III. This phenomenon is aggravated by immobilization which activates the so-called "sleeping afferent: chemoreceptors" and causes more firing and exhaustion of layers I-III of DH.

Eventually, the loss of plasticity of the DH cells results in a spontaneous ongoing stimulation of the spinal cord augmented by lack of inhibitory effect of the dead inhibitory granular cells in the substantia gelatinosa.

At this stage the main defense mechanism is the increasing concentration of dynorphin in the DH. However, the use of Morphine agonists (addicting narcotics) is apt to inhibit the formation of endorphins including dynorphin. This therapeutic factor accelerates the irreversible permanent damage, and leads to disturbance of plasticity, and failure to respond to treatment in late stages of RSD.

The picture is further complicated and the pathologic state is more fixed and irreversible due to the peripheral sensitization of the sensory nerves to systemic norepinephrine which eventually renders sympathectomy or nerve blocks useless (4).

The development of the WDR of Nathan and Roberts obviously renders any form of neurectomy, tractotomy or rhizotomy useless in the management of RSD(2,3).

PLASTICITY

Plasticity refers to the ability of the body to adjust a stressful stimulus. In acute stages of the disease, the immune system responds to counteract the assault to the internal environment. With the cessation of the stressful stimulus, the body has enough plasticity and recovery power to return back to its normal state.

However, if the disease becomes chronic, the distressful impulses become repetitive, and the immune system is disrupted due the persistence of the illness and/or improper injurious treatments, the complex chronic state of the disease permanently distorts the immune system response, and the body loses its plasticity to return back to its normal state.

This lack of plasticity is the result of the long term effect of distressful stimulus on the DNA structure in the nucleus of the cells that are responsible for providing the proper defense mechanism and to return back to normal after the cessation of the stimulus. The repetitive stimulation results in a transformation in the DNA genes, formation of newer genes (such as c-Fos and c-Jun). Eventually, the disease attains an irreversible state, and the pathologic condition becomes fixated.

In RSD, the disturbance of plasticity plays a major role in failure of permanent failure of treatment.

FACTORS RESPONSIBLE FOR DISTURBANCE OF PLASTICITY

The following factors play a major role in the disturbance of plasticity.

(i). Older age. It is well known that RSD is just as common between children and teenagers as in adults. However, children and teenagers have a far stronger force of plasticity, and can adapt, adjust, and compensate for damages caused by disease or by improper treatments.

(ii). Chronicity. It is a well-known fact (reported by Poplawski since 1983) that the success rate of treatment drops from 80% in the first six months of the onset of the illness down to less than 60% two years after the onset of the disease (5).

Realizing that there is such a reluctance on the side of the clinicians to consider or diagnose RSD, precious time is lost in the first 1-2 years before the disease is diagnosed and properly treated.

(iii). Anatomical factor**.** The causalgic (ectopic or ephaptic) form of nerve damage causing RSD has a more accelerated pathologic course and in a matter of weeks or a few months, the patient goes from stage I to III. The plasticity deteriorates far more rapidly in such patients (6). The best example is causalgia after amputation, or causalgia due to sympathetic nerve injury secondary to venipuncture (7,8).

(iv). Pre-existing injury. It is not at all uncommon for the patient to have suffered from a sympathetic nerve dysfunction with partial recovery pre-existing the second minor injury flaring-up the pre-existing condition. The repetitive trauma accelerates the course of disturbance of plasticity. One relatively common example of this condition is the development of RSD of disuse and overuse among riveters, court reporters, and assembly line workers who are exposed to an overuse and disuse work condition (6).

(v). Disturbance of inhibitory system of the central nervous system (e.g., DH of the spinal cord) due to an iatrogenic factor. Especially application of ice, braces, and unnecessary operations cause exhaustion of the inhibitory system and results in permanent lack of plasticity.

THE ROLE OF DORSAL HORN IN PLASTICITY

There are five distinct layers in the DH grey matter of the spinal cord. The first (marginal) and the second (SG) are the two superficial layers of the DH. These two layers receive the majority of the thermoreceptors, the mechanoreceptors, and the chemoreceptors input. The mechanoreceptors mainly terminate in the layers II and III whereas the small c-fibers of thermo and chemoreceptors mainly terminate in layer II. The disturbance of the mechanoreceptors is mainly responsible for the development of allodynia. The disturbance of thermo and chemoreceptors is mainly responsible for hyperpathia and eventual development of inflammation. Approximately 25% of the chemoreceptors are the "sleeping nociceptor" nerve fibers. They are usually inactive and they become active in atonic and accelerated fashion after the development of inflammation of RSD and especially after immobilization of the limb with the use of brace or cast.

The layers I and II show a higher concentration of SP. The layers III, IV, and V show a higher concentration of acetylcholine dynorphine. These deeper layers, III, IV, and V are mainly inhibitory in function. They balance and inhibit the input of pain in accumulation of SP in the superficial layers. The deeper layers IV and V are mainly somatosensory rather than neuropathic sensory nuclei.

Repetitive neuropathic sensory stimulation results in atrophy of inhibitory granular cells in the DH. The secondary loss of inhibition due to the atrophy of the granular cells allows larger input of the nociceptive impulses with secondary reflex stimulation of sympathetic efferent nerve fibers and development of ischemia, and cold skin surface. The hypoxia and ischemia result in further stimulation of the "sleeping nociceptors." The hypothermia of the skin further stimulates the low threshold modulation (LTM) small c-fibers with further formation of SP in the DH.

The repetitive, chronic, vicious circle mentioned above becomes aggravated and exaggerated with bed rest, inactivity, use of assistive devices, use of ice and Capsaicin, as well as unnecessary surgical procedure (6, 9).

The end result is irreversible aggravation of RSD, permanent damage and dysfunction in the DH of the spinal cord, and secondary development of inflammation as a major byproduct of sympathetic dysfunction.

With further deterioration of the above mentioned vicious circle, certain nerve cells in the layer V of DH become stimulated. These nerve cells indiscriminately respond to the noxious stimuli of any form (mechanical, thermal, or chemical) and result in the spread of the nonspecific pain response to adjacent levels of the spinal cord. These polymodal cells are being in discriminatory, and generate a WDR of pain response. They play a major role of the spread of the disease from one specific organ to larger areas such as the entire one or more limbs in the body. The disease then becomes not a focal disturbance of function, but a regional pathologic state. Hence, the proper terminology of complex regional pain syndrome (CRPS). One main complication of the above-mentioned disturbance of sympathetic modulation and plasticity is inflammation.

ORIGINS OF INFLAMMATION

Of the three major functions of the sympathetic system (control of vital signs, control of circulation and control of the immune system) in the long run the immune system disturbance plays a major role in inflammation, chronicity and intractability of the disease (10).

The disturbance of the immune system causes inflammation and confuses the clinician which leads the clinician to perform unnecessary operations such as surgery for the so-called tarsal tunnel syndrome, or carpal tunnel syndrome. The immune system disturbance causes inflammation in the involved region of CRPS, mimicking the above-mentioned types of entrapment neuropathy (10).

The above-mentioned operations only cause more inflammation and more rapid deterioration of RSD. The same is true for regional nerve blocks done in the area of nerve damage. The performance of so-called nerve blocks in the area of ectopic (causalgic) nerve damage aggravates the RSD. Here lies the contribution of infrared thermal imaging (ITI). The ITI identifies the ectopic area and warns the clinician to stay away and not to stick a needle or knife in the area of nerve damage (6, 11-13).

The immune system response is multifaceted. In earlier stages of RSD, a neurogenic plasma extravasation occurs. This was first reported by Mitchell in 1864 and later by Abram in 1990 (14,15).

The small c fibers (thermal receptor) and their cell body in DRG play a major role in this inflammatory response. The same inflammatory response causes neurodermatitis, edema, and the formation of SP peripherally. Eventually, this inflammatory response becomes chronic resulting in topical release of lymphocytes, degeneration of the mast cells and thickening of the wall of the arterioles with resultant vicious circle of further aggravation of RSD (16,17).

The use of ice results in hypothermia, and c-fiber response accelerates the inflammatory response with edema, damage and destruction of the axon and myelin sheath of the nerves (9,18).

The use of assistive devices (wheelchair, crutches, etc.) causes reduction of the somatic inhibition of the sympathetic system, and aggravation of inflammatory response. The released SP increases capillary permeability and releases histamine with initiation of inflammatory response (19). Secondary vasodilation and increased blood flow in the deep structures of the extremity causes weakness of the muscles and rarefaction of the bones (Sudeck's atrophy) develops.

The inflammation is not limited to a dermatome but is more regional and segmental involving the adjacent and remote segments involving wide areas of the spinal cord leading to "Neurogenic Inflammation" spread of the disease. This explains the remote inflammatory response seen in different parts of the body secondary to a regional RSD(20).

The inflammatory response is intermittent and needs not to be present at all times. It changes from day to day. In our experience, the inflammatory response is twice as likely reflected in past history rather than on present examination. Chelminsky, et al reported even higher incidence of inflammation recorded from past history rather than observed during the examination (21).

SKIN TEMPERATURE CHANGES

The inflammatory response results in an edema of different degrees (even to the extreme of elephantiasis). In early stages it causes warm red and dry extremity; in a matter of a few weeks the skin becomes cold, pale, hyperhidrotic, cyanotic and develops a brawny, milky, appearance (22).

In acute stage of the disease, a large number of patients suffer from hyperthermia in the involved area. This mainly reflects the permanent damage to the sympathetic nerve fibers in the center of the area of injury. This is simply a temperature leakage due to lack of vasoconstrictor response of the sympathetic nerves.

In subacute and chronic stages, a reflexive surround hypothermia develops. This lasts through the course of the disease, and becomes aggravated by use of ice and use of assistive devices (casts, wheelchair, etc.). In the later stages of RSD, iatrogenic hyperthermia develops because of two major factors:

(i). Repetitive, traumatic, sympathetic ganglia nerve blocks result in a virtual sympathectomy and temperature leakage (10-13).

(ii). Surgical sympathectomy results in the same type of hyperthermia. After a few years, the adjacent intact sympathetic nerve fibers tend to compensate for the temperature leakage due to sympathectomy, and the hyperthermia becomes focalized to the area of original injury. Some of the normalization of the temperature is also due to the principle of sensitization of the peripheral nerves to systemic norepinephrine with resultant vasoconstriction (Cannon Phenomenon). Eventually, the body compensates for the sympathectomy (6,10).

Sympathectomy is nothing but destruction and removal of the thermostat in the house just because the house is cold. Come summer, the house will be quite hot and the thermostat is not capable of counteracting the extra heat. Except for in young adults (soldiers during the war) which adapt to any condition because of their strong plasticity due to rich growth hormones and other hormones, sympathectomy in other patients is apt to fail. Its only indication is for people who are going to live less than five years (such as in diabetic vascular involvement) when sympathectomy is done as a palliative temporary treatment (6,10).

SUMMARY AND CONCLUSION

The sympathetic system is not hyperactive in RSD but is dysfunctional. The use of ice, assistive devices, surgical procedures, or addicting narcotics is apt to aggravate the dysfunction of the sympathetic system and in the long run is responsible for high percentage of treatment failure in such patients (6,9,10).

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