RESEARCH ON PURPOSE

Christopher Kent, D.C., FCCI

Neuroplasticity

In a recent issue of *Scientific American,* Michael M. Merzenich noted, "The brain was constructed to change."[1] This challenge to the conventional worldview that the mature adult brain is stable and unchanging — the only exception being the death of brain cells — has profound implications for the chiropractor.

As Gage stated, "Researchers first demonstrated that the central nervous systems of mammals contain some innate regenerative properties in the 1960s and 1970s, when several groups showed that axons, or main branches, of neurons in the adult brain and spinal cord can regrow to some extent after injury."[2]

The ability of the brain to change both anatomically and functionally is known as neuroplasticity. Clifford reviewed three types:

1. ***Experience-independent*** plasticity refers to changes which are not the result of environmental changes or influence.

2. ***Experience-expectant*** plasticity occurs when the brain uses input from the external environment to effect normal

2. Gage FH: "Brain, repair yourself." *Scientific American* 2002;289(3):47.

3. http://hcs.harvard.edu/~husn/BRAIN/vol6/p16-20-Neuronalplasticity.pdf

4. http://www.jvsr.com/archives/kent.pdf

5. Barge FH: "One Cause, One Cure." LaCrosse, WI. 1990.

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developmental changes in its structure.

3. ***Experience-dependent*** plasticity is when a modification to the internal or external environment produces change in a feature of the brain.[3]

Holloway explained how the brain reconfigures itself, and the implications of doing so:

"Change the input-be it a behavior, a mental exercise...or a physical skill-and the brain changes accordingly. Magnetic resonance imaging machines reveal the new map: different regions light up...

"[T]he brain can be extensively remodeled throughout the course of one's life, without drugs, without surgery. Regions of the brain can be taught to do different tasks if need be...This sort of thing will be a part of normal future life...healing plasticity can be driven by behavior."[1]

Vertebral subluxation may result in dysafferentation,[4] a process where aberrant afferent input results in qualitatively and quantitatively distorted perception of the external and internal environment. In 1996, I described how this could lead to dysponesis and inappropriate motor function. Today, we know the stakes are much higher-dysafferentation may result in anatomical and functional changes in the brain itself.

Dr. Fred Barge, in his book, "One Cause, One Cure" stated that the cause of disease is "The body's inability to comprehend itself and/or it's environment."[5] Such "comprehension" is dependent upon interference-free afferent input. This sculpts the brain, and as a result, our very sense of self.

References

1. Holloway M: "The mutable brain." *Scientific American* 2002;289(3):79.

FSCO offers scholarship money

All chiropractic students eligible

The Federation of Straight Chiropractors and Organizations (FSCO), pleased to have given away tens of thousands of dollars to students over the years through the John Stachurski Memorial Scholarship program, will this year be giving away thousands more.

Chiropractic students from any chiropractic college are eligible to receive this money and compete for several prizes, simply by writing a brief statement about a relevant chiropractic topic. This year, students explain their current involvement in the profession and share their vision for practice after graduation.

The scholarship program is just one of many ways the FSCO continues its commitment to protecting and promoting the non-therapeutic approach to the correction of vertebral subluxation.

"Assisting our students is one of the greatest things we can do to benefit our profession," said Dr. David McGonagle, chair of the FSCO Scholarship Committee. "We recognize how critical students are to the future of our profession and to the ability of all people to receive the care that is so desperately needed throughout the world."

Students interested in specific details should check with their school's financial aid office for information. The FSCO may also be contacted directly at 800/521-9856 or by going to the FSCO website at www.straightchiropractic.org. Entries must be e-mailed or postmarked by Sept. 15, 2003.

A Bonebrake

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Mustard oil
capsaicin

Reviews of the Literature

Spinal Learning: Central Modulation of Pain Processing and Long-Term Alteration of Interneuronal Excitability as a Result of Nociceptive Peripheral Input

MALIK SLOSBERG, D.C.*

ABSTRACT

The influence of nociceptive peripheral input on the response characteristics of spinal interneurons may result in long-term alterations of interneuronal excitability and modify their responses to subsequent stimuli. Such neuromodulation has been found to result in physiological changes including hyperalgesia, lowering of pain thresholds, expansion of receptive fields and changes in response behaviors of muscles. These types of alterations may contribute to clinically significant findings including muscle spasm, hypomobility, edema, chronic pain, recurrences in areas of previous injury and resistance to treatment. This article reviews studies concerning plasticity of response behaviors of interneurons including habituation, spinal learning, spinal fixation, neuromodulation and the effects of substance P. Potential clinical and chiropractic application are discussed and a brief review of clinically relevant studies of chiropractic adjustments are cited. (J Manipulative Physiol Ther 1990; 13:326–336).

Key Indexing Terms: Neuromodulators, Nociceptors, Substance P.

INTRODUCTION

A recent review article examined the impact of afferent input from articular and periarticular structures on muscle and sympathetic tone, postural reflexes, proprioception and articular pain (1). Additional work investigating the influence of these effects indicates that sensory articular patterns produced under normal conditions are markedly altered with tissue injury, trauma or inflammation (2–4) and that change in sensory input from articular structures under such conditions may result in alterations of locomotor function, sympathetic responses, proprioception and pain (1, 2, 5–7). Such changes may be due to the intensity and constancy of nonadapting nociceptive input, which occurs with tissue damage and contributes to diffuse and disruptive efferent response patterns (8–11).

The hypothesis that the aberrant motor and sympathetic responses are initiated and maintained by altered sensory input with tissue damage has been suggested by studies reporting an abolition of the reflex motor and sympathetic responses by injections of anesthetic into the joint generating the afferent input, or by destruction of sensory nerves transmitting the afferent pattern centrally from that joint by electrocoagulation, or by cutting the involved nerves (12–15).

Related questions which have stimulated much conjecture and investigation concern the mechanisms by which alterations of muscle and sympathetic tone may be maintained for extended periods of time, and the degree to which they may account for recurrences of musculoskeletal symptomatology in areas of previous injury that appear to have healed. These situations suggest some type of long-lasting alteration in response traits of the neurologic pathways in the involved region, so that a residual hyperexcitability or facilitation remains despite the eventual cessation of the initial nociceptive afferent bombardment. Both Denslow and Hassett (16) and Korr et al. (17) reported that facilitated motor and sympathetic regions may endure for prolonged periods of time. Korr reported cases of subjects demonstrating signs of sympathetic hyperactivity for 2½ and 4 years. Denslow and Hassett reported cases of sustained motor facilitation of 15 weeks and more.

Recent studies suggest that even when the nociceptive bombardment which initiated the facilitation has abated or is blocked by anesthesia, the hyperexcitable

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area may endure if the afferent barrage has been of sufficient intensity and duration. How then is such chronic facilitation sustained if not by a constant afferent barrage? This question is significant to clinicians administering manipulation because an understanding of these mechanisms may increase our insight into how chronic or recurrent musculoskeletal pain or joint dysfunction is initiated and maintained, and we may better understand how manipulation modifies such altered neurologic reflex patterns.

DISCUSSION

Plasticity in the Nervous System

To understand the neurologic consequences of tissue injury it is valuable to review the historical development of research in this area. Patterson (18) states that for many years the neurologic pathways between sensory receptors and neuromuscular junctions were considered to be "hard-wired relay mechanisms" which efficiently transmit neural impulses but are not affected by the input they transmit. The polysynaptic pathways involved were considered to be "passive transmitters of information" that were, themselves, unchanging and mechanical rather than "active or even reactive participants in information processing" (18).

More recently, Byrne (19) reviewed studies investigating the neural pathways as well as the cellular and synaptic alterations which may occur in response to afferent input, particularly if is is repetitive or noxious. Byrne's review suggests that such "biochemical and biophysical events occurring in specific neurons account for learning and memory" and that the simplest changes noted in response characteristics of neurons to repetitive input are those of habituation and sensitization (19).

Habituation and Sensitization

Response habituation is defined as a decreasing responsiveness to repetitive stimulation by the same stimulus. Response sensitization is defined as an increasing responsiveness to repetitive stimulation by the same stimulus. Both of these alterations are considered to be forms of behavioral plasticity (19, 20). Both decay spontaneously and are of short duration. If the stimulus is discontinued for a brief period of time and then resumed the neural response will return to its initial level. There does not appear to be any long-lasting alteration due to either habituation or sensitization. However, these short-term alterations indicate that neural pathways are capable of adapting and changing in response to neural input. Other studies investigating the neural mechanisms for the plasticity of behavioral responses to repeated stimulation suggest that response habituation and sensitization, as well as other alterations indicative of behavioral plasticity, involve interneuronal mechanisms (19–22). Groves and Thompson (20) as well as Thompson and Spencer (23) have reported that habituation is maximal when nerve stimulation is below maximum Group II threshold (selectively stimulating mechanoreceptors) and sensitization tends to predominate when group III and IV fibers are activated (nociceptor populations).

These forms of plasticity of behavioral responses may be adaptive mechanisms by which an organism responds to environmental changes. It is important to respond to repetitive noxious stimuli because it may cause progressive tissue damage, whereas repetitive innocuous stimuli may have no significant effects on the organism.

Spinal Learning

Associative learning is considered to be one of the simplest forms of learning in the nervous system. Byrne (19), Patterson (24) and Bolles (25) review the basic concepts of associative learning and classical conditioning. In associative learning the organism changes its response characteristics to a conditioned stimulus because it has been repeatedly paired with an unconditioned stimulus. A conditioned stimulus (CS), by definition, is considered to be a neutral stimulus which results in little or no neurological response when presented by itself after a few presentations. An unconditioned stimulus (UCS), by definition, consistently evokes a well defined response, felt to be an inborn reflex. By pairing presentations of a CS with an UCS, the subject begins to respond to the CS in a manner similar to its response to the UCS, i.e., a conditioned response (CR).

The persistence of the CR after training is called retention (19). The retention of the learned response is variable; some CR last brief periods, others for many hours, days, weeks or months (19, 24). The CR can be inhibited by the active process of extinction, repeatedly presenting the CS without pairing it with the UCS. Nevertheless, after extinction the conditioned response may be relearned quickly, often in only a few pairings of CS with the UCS (19, 24, 25).

Bolles (25), Patterson (24) and Shurrager and Culler (26) report that Pavlov maintained that associative learning was due to the formation of new synaptic connections. Furthermore, Pavlov proposed that asso-

ciative learning can occur only when the cerebral cortex is intact. He asserted that the lower centers of the central nervous system were incapable of associative learning (24, 26). Despite his assertions, however, more recent studies have demonstrated that spinalized cats (with a transected spinal cord; also called spinal cats) can change their response characteristics to peripheral electrical impulses of low intensity when they are paired with 50 volt impulses (27). The low volt impulses, by themselves produce very small responses from motor nerves—an almost imperceptible twitch. However, when paired with 50 volt impulse trains that produce a maximal response of the involved motor nerves (a forcible flexion withdrawal reflex) the response to the low volt impulses markedly increases until it resembles the response to the high volt impulses.

Byrne (19), Shurrager and Culler (26) and Patterson (24, 27) conclude that in spinal animals, involved spinal reflex arcs respond to pairings of CS-UCS in a way which seems to parallel some aspects of learning in the intact animal. Further research supports this belief. Durkovic presented pairs of CS and UCS in one group, unpaired CS and UCS in another and CS alone in a third group of spinal cats. He concludes that paired stimulation resulted in rapid facilitation of the flexor reflex to the CS. Such facilitation was not observed in the other groups. He concludes that his findings meet the criteria for the operational definition of classical conditioning (28). By using various interstimulus intervals and backward pairings of CS and UCS, Patterson tested nonassociative, additive and pseudoconditioning effects and concluded that the learning of the CR was dependent on the appropriate interstimulus interval and was, therefore, a form of associative learning (27, 29). Patterson (29) and Steinmetz et al. (30) report a series of experiments to determine where the site of associative learning occurred and deduced that the location is not within the sensory receptors of the skin being stimulated, because the skin can be anesthetized without loss of the CR (27). In addition Steinmetz et al. determined that the retention did not occur at the ventral roots, muscle or the neuromuscular junctions, because severing the ventral roots following the conditioning procedure resulted in loss of the CR (30, 31). The authors concluded that the site of associative learning is within the interneurons of the spinal reflex pathways.

In addition, Patterson maintains that the learning is not due to the formation of new synaptic connections as originally thought by Pavlov, but rather to modifications of synaptic connections that already exist. Positive results, therefore, become not the acquisition of a new response entity but the alteration of an existing response (24). Byrne refers to conditioning procedures in which the CS initially produces a small response similar to that evoked by the UCS, and the enhancement of this response due to pairings of the CS with the UCS as alpha-conditioning, also a form of classical conditioning (19).

Shurrager and Culler reported a mild tail shock or tail pressure in spinalized dogs (which produced only a small twitch) could produce a much more prominent contraction after pairings with an UCS of strong hind-paw shock. Furthermore, their studies indicated that the portion of the cord necessary for these results consisted of only a few segments, probably only one or two (26). Light and Durkoviac report that in spinal animals the response to the CS was unchanged if the UCS stimulated only mechanoreceptors. Moderate increases occurred, if the UCS stimulated A-delta fibers (mostly fast pain), but exhibited maximal response increases if C-fiber (mostly slow pain) were excited by the UCS (32).

These findings indicate that the spinal interneuronal pathways are not only capable of temporary, adaptive alterations in their response characteristics to peripheral stimuli, but are also capable of a form of associative learning which has good retention and may not spontaneously decay. In addition, the results indicate that rather than being hard-wired, passive transmitters of information, these pathways may learn to modify their response to input in ways that may be long-lasting and, therefore, may influence the response in these interneuronal pathways to subsequent input. Furthermore, these alterations appear to occur most markedly with noxious sensory input.

Long-Term Alterations Due to Sensory Stimuli: Experimentally Induced Central Lesions

Studies examining long-term alterations of neural responses to sensory stimuli, as opposed to the short-term changes of habituation and sensitization, date back to the 1920s. Patterson (24) states that DiGiorgio was the first to report that experimentally produced selective damage to regions of the cerebellum in dogs could induce flexion in one limb and extension of the contralateral limb, and that these postural alterations would persist following spinal cord section if 3–4 hours were allowed to lapse before sectioning. Chamberlin et al. (33, 34) noted that it required a minimum of approximately 45 minutes from the time of lesion to the time of spinal section for the flexed posture to be retained after spinal section. If the animal was left intact for a period of approximately 45 minutes after the

cerebellar insult before spinal section was performed, then after section the flexion would be retained despite the fact that the lesioned cerebellar area was now severed from the neural pathways affecting the involved limb. If spinal section occurred within 35 minutes after the cerebellar damage was induced then the flexion was lost and the limbs became flaccid as is usually the case with spinal transection.

Guyton states, "When the spinal cord is suddenly transected, essentially all cord function, including cord reflexes, immediately become depressed to the point of oblivion . . . After a few days to a few months of spinal shock the spinal neurons gradually regain their excitability" (35). The retention of an abnormal posture, known as "spinal fixation" (24), induced by lesion of an area no longer neurologically connected to the motoneurons responsible for the posture, as well as the maintenance of local neuronal activity instead of the normal flaccidity as the result of spinal shock, were both considered to be remarkable. The time required for this change to be "fixed" indicates that some mechanism for retention requiring a definite period of time to occur was involved. This suggests some kind of neuronal, synaptic or cellular mechanism for memory within the reflex pathways of the spinal cord. Steinmetz et al. state "the retention of postural asymmetries after spinal cord section was dependent on biochemical alterations that occurred during the spinal fixation time" (36). Both Groves and Thompson (20) and, more recently, Byrne (19) review the many studies and theories of neuronal and synaptic mechanisms which may account for these adaptive patterns of behavioral plasticity.

Long-Term Alterations due to Sensory Stimuli: Induction by Peripheral Lesions

In other studies, it has been demonstrated that long-term alterations of spinal reflex patterns can be induced by noxious, repetitive peripheral stimulation as well as from experimentally induced lesions of the central nervous system (37–40). Within the dorsal horn there are two general types of interneurons capable of transmitting nociceptive input: nociceptive specific neurons and nociceptive nonspecific or wide dynamic range neurons, also known as multireceptive neurons (41–43). The wide dynamic range (WDR) neurons receive input from nociceptors as well as mechanoreceptors (41–43). Besson and Chaouch state that the WDR neurons respond to a variety of stimuli with a progressive "increase in the frequency of (their) discharge" as the stimuli become progressively more noxious and thus can report and discriminate between innocuous and noxious stimulation (42). Roberts (43) contends that trauma to peripheral tissues, which activates C-fiber nociceptors, excites WDR neurons in the dorsal horn of the spinal cord and causes them to become more responsive to all subsequent afferent input. He proposes that "if this sensitization of WDR neurons is persistent over time, then the WDR neurons will continue to give a vigorous response to mechanical stimulation of A-fiber mechanoreceptors even after healing is complete, leading to touch-evoked allodynia." Roberts also maintains that A-fiber mechanorectors can be activated by sympathetic efferent stimulation "with the same painful result."

Frankstein (36) reported that injecting turpentine into the footpads of cats produced typical inflammatory and behavioral responses characteristic of pain, including a flexion withdrawal reflex. These initial reactions gradually subsided and normal locomotion returned. However, with decerebration, after the inflammatory injury induced by the turpentine was healed, the flexion returned. This suggests that while the peripheral irritation which induced the flexion had stopped, long-lasting alterations had occurred in the spinal reflex circuits which were compensated by the cortex to produce normal locomotion. With the cortical compensation gone, the abnormal reflex pattern was restored. Frankstein interpreted this to indicate that the injury produced "pathological excitation" in the nervous system which persisted even though the peripheral irritation which initiated it had ended. Moreover, the evidence indicated that the organism was "forced to compensate to conceal the traces of excitation in the nervous system" (37). This compensation was removed with decerebration and the afferent-induced excitability returned. Frankstein interpreted these findings to indicate that neural pathways may become excited by noxious stimulation producing long-term alterations in their response characteristics which may persist though the noxious stimulation has ceased.

Patterson and Steinmetz report a recent study in which groups of rats received noxious electrical stimulation for durations of 45, 60 or 90 minutes to the right hind leg (44). Five minutes after stimulation the degree of induced flexion was measured by suspending weights to the limbs and determining the amount required to remove the flexion. Afterwards the rats were divided into groups allowed 24, 48 and 72 hour recovery periods. At the end of these times the rats were examined for the amount of flexion remaining and then received spinal transections at T7. Five minutes posttransection the degree of flexion was measured by once again suspending weights from the involved limb. The ani-

mals showed little or no locomotion deficits during the recovery period. Of the 81 rats, only two displayed flexion at the examination immediately before spinal transection. After spinal section, however, there was a reappearance of flexion in many animals in each group and a significantly higher reappearance of flexion in the groups initially stimulated for 60 and 90 minutes. The authors also note that there were no significant differences between recovery period groups when postsection asymmetries were analyzed. They conclude that short-term noxious stimulation can produce long-term spinal circuit changes resulting in either mild spontaneous output or residual, subliminal hyperexcitability within the neuronal circuits involved.

These focal areas of facilitation are apparently retained despite periods of normal activity. The authors suggest that during the recovery period the animals are capable of normal locomotion as a result of compensation by higher motor centers. When this supraspinal control is removed by spinal section, however, the hyperexcitability becomes apparent and flexion recurs despite the fact that one group's recovery period was three times longer than another's. These findings suggest that such hyperexcitability may be long-lasting, altering the involved neurons response to subsequent stimuli, and producing "changes that are not easily removed" (44).

Hoheisel and Mense studied the size and thresholds of the receptive fields (RF) of dorsal horn neurons responding to noxious input from deep tissues in cats (45). They selected dorsal horn neurons with dual receptive fields, one RF in the semitendinosus (ST) muscle and another in gastrocnemius-soleus (GS) muscle. After determining the usual size and thresholds of these RFs, bradykinin (in a dose reported to excite muscle nociceptors and, therefore, considered to be painful) was injected into the RF of the ST muscle. After injection the properties of both RFs were again tested. The dorsal horn neuron with the injected RF in the ST demonstrated a lowered threshold for stimulation so that it now responded to innocuous pressure and its RF, which previously included only a small area of the muscle now was expanded to encompass the entire ST muscle. In addition, the noninjected RF in the GS muscle likewise showed a decrease in mechanical threshold. A second injection of bradykinin produced similar but more prolonged changes of RF size and threshold.

Hoheisel and Mense noted that the decrease in threshold in the injected RF may be attributable to "sensitization of nociceptors, but the enlargement of the RF and the lowered threshold of the RF in the GS muscle cannot be explained by such a mechanism. In addition, the electrical threshold of the (dorsal horn) cell upon stimulation of the sciatic nerve likewise decreased after the bradykinin stimulus" which could not have been due to sensitization of the nociceptors. The authors interpret these findings to indicate that "a short-lasting noxious stimulus to the deep tissues is capable of changing the response behavior of individual dorsal horn neurones with deep input for long periods of time . . . and probably reflects an increase in excitability of the dorsal horn neurones." Such alterations "speak in favor of a central mechanism . . . A speculative explanation would be that the small-diameter deep afferent units release neuropeptides at their spinal terminations which induce slow postsynaptic potentials in dorsal neurones and thus modulate the excitability of the cells" (45).

The Flexion Withdrawal Reflex: Alterations with Injury or Noxious Conditioning Stimuli

Woolf and Wall report that injection of mustard oil, an irritating substance which induces a local inflammatory reaction, produces long-lasting facilitation of the flexion withdrawal reflex in response to a standard pinch stimulus (46). The flexion withdrawal reflex is normally a remarkably stable response. When repeated for hours, the action potentials elicited in response to a standard pinch stimulus are very reproducible (47). Woolf suggests that such a stable response provides a particularly useful way of measuring any disturbance or alteration in the functional performance of the spinal cord (48).

Under normal conditions the flexion withdrawal reflex is classified as a phasic avoidance response. It adapts rapidly to a standard peripheral noxious pinch stimulus, exhibiting a brief burst of activity with only a short afterdischarge in the involved flexor motoneurons. This results in a brief flexion withdrawal response (47). After injury, an experimentally induced conditioning stimulus of mustard oil, or a brief (20 seconds) electrical stimulation of sufficient intensity to stimulate C-fibers, the flexion withdrawal reflex response characteristics change markedly. The threshold falls to much lower levels so that previously innocuous stimuli which, under normal conditions, do not produce a flexion withdrawal response may now produce one (40). Furthermore, Woolf reports that the flexion reflex itself, becomes greatly exaggerated to supramaximal stimuli so that instead of a 1 second response, the flexion may be maintained for up to 150 seconds (49). In addition, Wall and Woolf found that the threshold for the flexion withdrawal response in the contralateral limb is also

lowered, suggesting that the alteration in response characteristics is mediated, at least in part, by changes in the interneuronal pathways of spinal cord (50). Finally, Woolf and Wall report that mustard oil injections in the skin, muscles and joints, all produce prolonged excitation; however, the most effective in producing prolonged excitability changes were the result of stimulation of the joint afferents (46).

Woolf and Wall found that capsaicin, which selectively damages C-afferent fibers without harming myelinated fibers, used before the conditioning stimulus of mustard oil, completely blocked the excitability increases which usually result from mustard oil injection (46). When lignocaine, an anesthetic, was injected before the mustard oil "neither the local anesthetic nor the subsequent mustard oil produced any effect on the flexor reflex." However, when lignocaine was injected 30 minutes after the mustard oil injection, it "failed to influence the time course of the facilitation" (46). The authors conclude that noxious stimulation of sufficient intensify to activate C-afferent input generates "a heterosynaptic, prolonged facilitation" and "indicates that an ongoing afferent barrage is not required to sustain the excitability changes." Wall and Woolf report similar findings when an anesthetic is applied to an experimentally induced neural injury: "the central effects were initiated by the injury discharge but not sustained by any on-going afferent barrage by showing that local anesthesia of the cut nerve after 20 min did not alter the subsequent prolonged central facilitation" (50).

Cook et al. found that although the flexor withdrawal reflex becomes facilitated by the use of a conditioning electrical stimulus to stimulate C-fibers or injection of mustard oil, the monosynaptic myotatic (stretch) reflex elicited by Ia afferents to the same flexor motoneurons responsible for the flexor withdrawal reflex is unchanged (51). The authors interpreted these findings to indicate that the postconditioning excitability occurs within the polysynaptic interneuronal pathways and not at the motoneurons. Furthermore, the authors contend that the facilitated flexor withdrawal reflex is not due to increased afferent terminal excitability of the nociceptors entering the dorsal horn stimulating the interneurons. They conclude that the facilitation occurs within the polysynaptic interneuronal pathways and not at the motoneurons or at the sensory receptors (51).

Substance P and Neuromodulation

In a recent review article, Woolf explains that our appreciation of long-term afferent induced central excitability has increased because of our understanding that C-fibers may not only release fast transmitters of pain in the dorsal horn, but also slow transmitters which produce prolonged effects. Substance P and other neuromodulators have the capacity to produce changes that last for seconds, minutes or even hours (48). Furthermore, Woolf found that localized thermal or chemical tissue injury results in long-term alterations in the thresholds and excitability of the flexor reflex, both ipsilateral and contralateral, at the site of injury for up to 6 weeks (49). He also reported that although the immediate response to substance P release is subthreshold, it alters the way in which the neurons respond to subsequent input (48). This alteration in the response behavior of second order neurons may account for the hyperalgesia which frequently accompanies tissue injury; After tissue injury, normally innocuous stimuli may be perceived as painful.

Woolf and Wiesenfeld-Hallin also conclude that in order for long-term changes of response characteristics in the spinal cord to occur, the peripheral stimulus must be of sufficient intensity to stimulate C-fiber nociceptors (52). Their findings suggest that in addition to transmitting information concerning the location and intensity of pain, C-fibers, by the release of neuromodulators, such as substance P, act diffusely on second order neurons of the dorsal horn to produce "long duration subthreshold modulations of their target neurons excitability to subsequent stimuli" (50).This is consistent with the findings of Urban and Randic, who found that substance P, released from C-fiber terminals in the dorsal horn, appears to be responsible for the slow and prolonged excitation of interneurons of the dorsal horn (53). In their review of peripheral and central substrates of nociceptive input, Yaksh and Hammond cite many sources further supporting the findings that substance P has a potent, long-lasting, general depolarizing effect on dorsal horn neurons sensitive to nociceptive input. In addition, they report that substance P has an extremely potent depolarizing effect on spinal motor neurons (54). Henry (55) also reports that substance P selectively excites dorsal horn neurons responsive to nociceptive input. He states that application of substance P to spinal interneurons by microiontophoresis results in a strong and prolonged excitatory action on nearly half of the neurons tested in the lumbar spinal cord of the cat. He concludes that substance P acts as a neuromodulator of excitability of afferent pathways producing an elevation of background discharge rate increase in producing an elevation of background discharge rate, increase in peak firing to heat stimulus, and prolonged duration of afterdischarge.

Badalamente et al. (56) found that substance P, which is synthesized in the cell bodies of dorsal root ganglia,

is produced in increased amounts, and increased quantities of substance P are released from synaptic terminals of the C-fibers in the substantia gelatinosa of the dorsal horn after experimentally induced mechanical stimulation, designed to simulate compression of the dorsal root by an intervertebral disc prolapse. Additionally, the authors state, "the strong excitatory action of substance P might have a functional significance as a sensitizer or modulator of pain over a long period of time." They postulate, that this may be one of the mechanisms by which disc prolapse may produce the protracted pain of sciatica.

Woolf suggests that physiologic pain may be associated with inflammation, and later, alterations in spinal neuron response characteristics due to neuropathic changes in reaction to noxious conditioning stimuli. "Chronic inflammation may, with time, induce alterations in the nervous system (either peripheral or central) changing inflammatory pain to neuropathic pain, such that removal of the inflammation does not necessarily remove the pain" (47). Woolf continues, "a constant barrage of abnormal inputs may induce permanent changes in the circuitry of the nervous system" (47). Besson and Chaouch (42), in their recent review article, report that the local erythema which occurs with inflammatory changes at a site of injury is a result of vasodilation, only induced if the simulation is intense enough to activate C-fibers. They state that during activation of unmyelinated nociceptors "substance P will be released both locally and at a distance via axon reflexes. This peptide can induce vasodilation . . . substance P so liberated can cause histamine release from adjacent mast cells, which produces vasodilation and activates or sensitizes the surroundings nerve endings." Yaksh and Hammon cite several studies corroborating substance P's impact as a mediator of neurogenically evoked extravasation (54). Both Levine et al. (57) and Lotz et al. (58) have also reported that the peripheral release of substance P from nociceptors may actively contribute to neurogenic inflammation.

Although the content of this article concerns long-term alterations of interneuronal excitability as a result of nociceptive peripheral input, it is important to note that other forms of neuromodulation, reducing the central transmission and impact of peripheral nociceptive input as a result of "segmental afferent A-fiber mediated inhibition" (59) and supraspinal modulation (42) may also occur and be of clinical use. There is an extensive literature beyond the scope of this article that examines the physiological and clinical features of gating mechanisms (60–62) and counterirritation (7, 63). The latter have recently been reviewed by Besson and Chaouch (42) and Woolf (64).

Interpretations of the Above Studies

All of the above findings suggest that noxious peripheral stimuli may be capable of inducing long-term facilitation of spinal interneurons. Woolf is probably correct in proposing that conditioning noxious input of sufficient intensity and duration acts like a trigger to increase interneuronal excitability, and may result in a permanent resetting of some of its neural elements following a noxious trigger (65). In addition, the afferent-induced central excitation persists long after the initiating stimulus has ceased and may influence responses to subsequent input. Wall states, "there are long-acting mechanisms which control excitability and that part of the pathology of pain is the setting of these mechanisms at incorrect levels of excitability . . . A prolonged afferent barrage from one source has changed the way in which the central nervous system handles an input from another source" (66). Patterson and Steinmetz propose that "the result of altered inputs to the reflex pathways of the spinal cord may be to produce changes which are not easily removed and that the effect of such changes may be to insure increased susceptibility to recurrence for at least hours, days, or months after the acute problem is resolved. At present it is unclear whether the effects of severe alterations produced by intense patterns of input to reflexes can be completely reversed" (44).

While it is evident that tissue trauma may induce local sensitization of nociceptors, reducing thresholds and producing hyperalgesia (45, 48, 67) the aforementioned studies indicate that tissue trauma and inflammation not only produce a change in the sensory pattern generated from the region of injury, but that this altered pattern of afferent input, in particular the C-fiber nociceptive input, and release of substance P may result in prolonged facilitation of interneurons. Such changes, which may endure long after the noxious input has subsided, may affect the involved interneurons response to subsequent input. Patterson has termed such an alteration within the spinal cord as a "neural scar" (27).

Patterson proposes that once the response to the CS is learned, the response may be retained over long periods of time and may not show appreciable spontaneous decay (18, 24). He postulates that some form of "memory" in terms of cellular, synaptic or biochemical alterations in response to sustained noxious input may generate a prolonged reflex hyperexcitability in the spinal cord. Woolf agrees, stating, "it is conceivable that long-term afferent inputs may produce permanent alterations in the properties of some central neurons . . . also that the level of activity in the spinal cord at any given time may be partly determined by events that

occurred some time before. The spinal cord, therefore, has a 'memory' of some of its previous inputs" (68).

Such focal areas of interneuronal facilitation may be responsible for recurrences, chronic pain, hypomobility and other forms of somatic dysfunction. In addition, Patterson and Steinmetz suggest that the areas of facilitation in the paraspinal regions reported by Denslow et al. (4, 16, 69, 70) may be clinical manifestations of areas of spinal neuronal reflex hyperexcitability probably secondary to previous noxious conditioning stimulation, such as earlier trauma. Such previous triggers may have initiated these long-term alterations of reflex hyperexcitability which persist, far outlasting the noxious afferent input which triggered them.

Possible Chiropractic Implications

The research discussed in this review article may have clinical significance for chiropractic. However, to jump from the results of the above data to chiropractic application requires a considerable speculative leap and such leaps are all too common in chiropractic (71–73). There remains much to be investigated before such application is well substantiated. Nevertheless, many authors have found that afferent changes induced by experimental trauma to paraspinal structures in animals may contribute to long-term alterations of local reflex pathways, possibly producing muscle spasm, immobility, edema, chronic pain, recurrences or resistance to treatment. Although the above literature is certainly not definitive in confirming clinical applications, it does tend to support such theories. Trauma may not only produce alterations in sensory neurologic patterning but may also result in altered muscle tone, mobility and sympathetic responses (1–2, 5–7, 10, 74, 75).

Patterson and Steinmetz found that spinal circuit changes of hyperexcitability induced by peripheral noxious input may remain despite prolonged periods of otherwise normal activity. Furthermore, they believe "there may be no necessity for ongoing afferent input to maintain the output patterns associated with . . . some forms of somatic dysfunction. In fact, once the afferent disturbance . . . becomes either sufficiently strong or long lasting, the reflexes themselves may well become participants in the maintenance of the symptoms . . . when the motion disorder, muscle tension . . . or other initiating disorder is removed, much of the attending excitability of the polysynaptic reflex paths will subside leaving either the mildly active spontaneous output or the 'neural scar' of hyperexcitable but subliminally excited neurons which will respond with abnormal amounts of activity to additional stimuli." The authors go on to say "much of manipulative therapy is aimed at decreasing . . . overactive neural input, thus allowing the reflex activity to return toward normal" (44).

Like many authors investigating spinal manipulative therapy (SMT), Patterson and Steinmetz speculate that if SMT is able to reinstitute mobility, normalize muscle tone and return afferent articular patterns back toward normal, as some recent research suggests, then it may be able to dampen or reduce such hyperexcitable neuronal pathways. "If reflex excitability can be increased, periods of normal or even subnormal input should tend to restore the reflex to its normal excitability range. Thus, manipulative therapy which tends to restore free motion, reduce muscle tension and so forth, and thus decrease abnormal and overactive afferent input, should at least allow the affected reflex paths to regain more appropriate excitability levels" (44).

CONCLUSION

Although it is beyond the scope of this paper to review all of the relevant clinical data examining the physiological and clinical effects of spinal manipulative therapy (SMT), it is worth noting that several recent studies on electrical activity in paraspinal muscles by Thabe (15) and Shambaugh (76) suggest that SMT may be capable of reducing excitability levels of local musculature when a manipulative thrust is applied to spinal motion segments. Moreover, as Shambaugh concludes "adjusting produced significant reductions in muscle activity in the back muscles (and) is consistent with what would be expected if vertebrae were changed from a hypomobile state to a more normal, moveable state" (76). Other recent studies investigating effects of SMT on range of motion (ROM) suggest that ROM may be increased as a result of SMT (77–82). A recent and well designed study by Nansel et al. investigating the effectiveness of cervical adjustments on goniometrically assessed cervical lateral flexion asymmetries found that subjects who received adjustments on the side of the most restricted end-range demonstrated a "dramatic reduction of asymmetry magnitude" while those subjects that received no intervention or only "set-up" procedures demonstrated unchanged post-testing asymmetry magnitudes (83). While it is certainly premature, at this point in time, to conclude that SMT may alter, reduce or reverse the nociceptive patterns that may result in possible central excitability triggered by trauma, nevertheless, recent papers examining the forces and effects of SMT on sensory receptors and analgesia suggest that SMT may be capable of influencing articular patterns of neurologic input (2, 7, 10, 14, 84–94).

It is essential to recognize that clinical research investigating the above phenomena is still in its infancy,

and it is important to acknowledge that this may be a fertile area of future inquiry.

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