Pain Projection Pathway

glutamate, substance P

Dorsal root ganglion

GABA

glutamate, substance P

Spinal Nerve

Spinal Cord

Path of DRR excitation from peripheral input

Nociception: New Understandings and Their Possible Relation to Somatic Dysfunction and Its Treatment

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Abstract Efforts to explain the underlying pathophysiology of somatic dysfunction have emphasized the role of the somatic and autonomic motor systems. Evidence reviewed here indicates that sensory, dorsal root neurons may also act in a motor fashion to contribute to peripheral changes that may be involved in somatic dysfunction. The peripheral effects of antidromic activity in sensory nociceptive neurons include neurogenic inflammation and may be triggered from peripheral inputs in a reflex fashion called dorsal root reflexes, or by descending activity from portions of the brain known to be activated by parts of the brain which process emotions. These developments may bring a broader perspective to the understanding of the origin of somatic dysfunction.

Key Words somatic dysfunction, dorsal root reflexes, nociception

Somatic dysfunction (SD) has been a central focus of osteopathic manipulative medicine from its beginnings. Two of the major theoretical contributions of recent decades regarding somatic dysfunction are those of Korr,[1] who emphasized the role of proprioceptors, and of van Buskirk,[2] who emphasized the role of nociceptors. In his article, van Buskirk discusses earlier theories that emphasized changes of flows of body fluids and changes in connective tissues. As he points out, these flows and changes are undoubtedly involved, but because of the time course of SD and its response to treatment, the search for primary triggers leads to the nervous system. More recently Willard has extended the nociceptive model by describing the links between nociception, the neuroendocrine immune system and somatic dysfunction.[3]

Traditional views have assumed that the neuromuscular changes associated with somatic dysfunction are mediated by altered motor output of the spinal cord via the somatic and sympathetic motor systems. Recent evidence indicates that changes in the periphery may also be mediated by signals passing from the spinal cord to the periphery on sensory neurons.

Organization of the peripheral sensory nervous system.

The peripheral sensory nervous system is roughly divided into two large groups of fibers based on their axon size and function. Large fibers, which arise in encapsulated sensory endings, have large myelin sheaths and conduct impulses rapidly. Their activity is conducted to the spinal cord, specifically to the ventral horn for reflexes such as the myotatic reflex, and to the large dorsal and lateral ascending tracts. Activity in these systems gives us such sensory modalities as discriminative touch, vibratory sense, and position sense.

Conversely, small fibers, which arise as naked nerve endings, have delicate sheaths but little or no myelin. As such, they conduct impulses slowly and are involved in warning systems. Activation of these small fibers usually requires noxious stimuli, and this event is termed nociception. These fibers are called "primary afferent nociceptors," or PANs. Impulses generated in a PAN are conducted through the spinal nerve back to the dorsal horn of the spinal cord. Our perception of nociception often is that of pain; however, pain is a perception, while nociception is a mechanical event. The two processes can be disassociated.

Sensory neurons can act like motor neurons.

It has long been known that some PAN endings in the skin and elsewhere in the periphery can release peptides that cause local responses. In other words, they act in a motor fashion. This phenomenon is well known as part of the axon reflex, in which, when one branch of a nociceptive afferent in the skin is activated by a noxious stimulus, action potentials (APs) travel not only into the spinal cord to register pain, but into the other peripheral branches of the neuron in the skin, where they
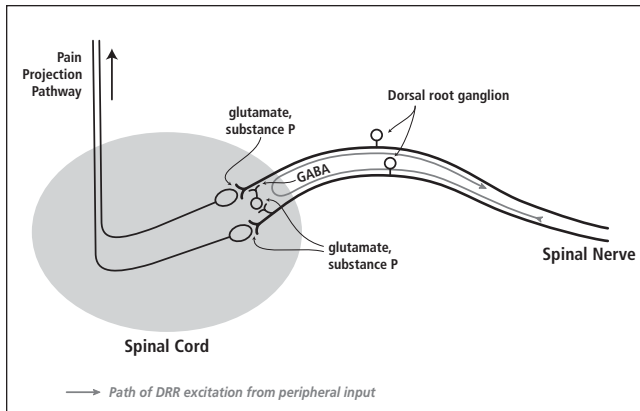
Figure 1. Pathway of the dorsal root reflex. Action potentials are generated peripherally in one of the two PANs shown and activate fibers of the pain projection pathway and interneurons within the cord. The interneurons, in turn, release GABA onto the endings of other PANs, causing the primary afferent depolarization (PAD). Low amplitude PADs reduce pain sensation by presynaptic inhibition; high amplitude PADs reach threshold to excite PANs, triggering action potentials that propagate to the periphery, where they release substances including substance P and CGRP, which promote neurogenic inflammation.

release substance P and calcitonin gene-related peptide (CGRP). These substances are responsible for the spread of the wheal of vasodilation from the site of injury to the surrounding skin, ie, for spreading the inflammatory response.

What has now become clear is that action potentials can be generated in the endings of sensory neurons within the spinal cord through axo-axonal connections. Axons of interneurons form synapses on the axons of primary afferents coming in from the periphery.[4] Activity of these interneurons may be triggered from other sensory inputs from the periphery[5] (Figure 1), or by descending signals from the brain stem[6] (Figure 2). Because they were first observed in response to the stimulation of other peripheral nerves, they were given the name, dorsal root reflexes (DRRs).[7]
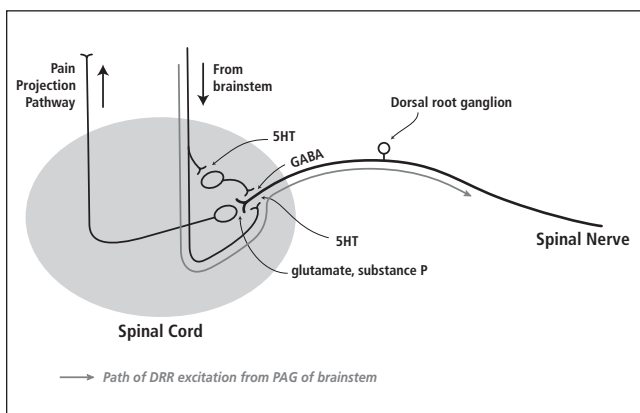

Figure 2.

Action potentials generated in PAN endings within the cord travel to the periphery. The effects they have in the periphery vary. For instance, nociceptive neurons excited centrally release substance P, CGRP, and somatostatin in the periphery causing neurogenic inflammation.[8] Work with invertebrates has provided

evidence that stretch receptor sensitivity may be influenced by antidromically conducted APs on sensory neurons that innervate these receptors.[9] It is possible that vertebrate stretch receptors, namely muscle spindles, may prove to be similarly affected, providing a second means, in addition to the gamma efferent system, by which the sensitivity to muscle stretch may be varied.

What mechanism within the spinal cord initiates motor activity in sensory neurons?

GABA is a transmitter substance that causes depolarization of the afferent (sensory) nerve endings within the cord. This depolarization is called a primary afferent depolarization (PAD). $GABA_a$ receptors on these endings are Cl- channels, which open in the presence of GABA. When Cl- channels open, the ending depolarizes. If the depolarization is sufficient to bring the sensory nerve to threshold, APs are generated and travel antidromically from the spinal cord to the periphery.[8]

For a more in-depth explanation of of this process, refer to the text box on page 14.

Motor activity in sensory neurons can cause neurogenic inflammation.

Evidence suggests that much of the pain and swelling of arthritis arises from a positive feedback cycle involving dorsal root reflexes. In arthritis that has been experimentally induced in rats by injection of carageenan into the knee joint, high level activation of peripheral nociceptors (C-fibers) sends APs into the spinal cord. In the cord these impulses activate projection fibers which carry that information to the brain. But they also activate interneurons that release GABA onto the presynaptic endings of these and adjacent C-fibers.[5,8]

At low intensities of afferent nociceptive inputs, the low level release of GABA probably has anti-nociceptive effects, mediated by presynaptic inhibition. At high levels of nociceptive input resulting from the carageenan injection, sufficient GABA is released to cause suprathreshold depolarizations, which generate dorsal root reflexes. The effect of antidromic activation of C-fibers is to release substance P and CGRP in peripheral tissues, where they enhance the inflammatory response, contributing to hyperalgesia. This is referred to as neurogenic inflammation. Interruption of this positive feedback cycle by application of the GABA antagonist, bicuculline, locally within the dorsal horn of the spinal cord, inhibits efferent activity and reduces knee inflammation (swelling, hyperalgesia, and knee temperature).[8] These experiments indicated that strong nociceptive input from the periphery contributes to the inflammatory response through this neural circuit.

Central activation of primary afferent depolarization links emotions and inflammatory processes.

Dorsal root reflexes can be generated, not only by peripheral nociceptive input, but by descending activity from the brain.[6,13] Electrical stimulation of the midbrain periaquadctal gray (PAG) in rats elicits depolarization of the endings of primary afferent

How does GABA, an inhibitory transmitter, cause excitation in primary afferent endings in the spinal cord?

First let us consider how GABA causes inhibition, as it does at many synapses. In many cells Cl- is passively distributed, ie, it is not actively transported across the cell membrane. This explains why the concentration of chloride is lower inside cells than in the extracellular space. Cl- is repelled from the cell by the inside negativity of the cell established by the Na+/K+ pump-leak system. Under these conditions, Cl- is at equilibrium; its equilibrium potential, calculated from the Nernst equation, is the same as the actual membrane potential. Cl- conductance acts to keep the membrane potential at or near its equilibrium potential.[10] It acts as a shunt, or short, to attenuate any deviation from resting potential. For instance, increased postsynaptic Cl- conductance from the inhibitory postsynaptic action of GABA on motor neurons decreases the amplitude of excitatory postsynaptic potentials occurring simultaneously in the cell. The inhibitory action of GABA does not necessarily involve hyperpolarization; the increased Cl- conductance caused by GABA simply counteracts, or attenuates, the depolarizing effect of excitatory transmitters.

Now let us consider how GABA causes excitation. In some cells, such as primary afferent neurons, Cl- is not passively distributed. In these cells, as in the cells of the thick ascending limb of the kidney, Cl- is actively transported into cells by a Na+/K+/2Cl- transporter, a coupled transporter which drives Cl- into the cell, driven by the Na+ concentration gradient across the cell membrane. In this case, the equilibrium potential for Cl- is less negative than the resting potential of the cell. When Cl- conductance is increased, Cl- flows out of the cell, causing depolarization toward the Cl- equilibrium potential.[11] This depolarization in primary afferent endings is called the primary afferent depolarization (PAD). If the PAD reaches threshold, APs are generated and travel antidromically to the periphery.

Is the action of GABA on primary afferents always excitatory?

No. Primary afferent depolarizations which are subthreshold for APs are inhibitory, not excitatory. Subthreshold PADs can actually block the passage of orthodromic APs coming in from the periphery, or at least attenuate their amplitudes as they travel into the spinal cord to the nerve endings where they cause transmitter release. APs of reduced amplitude reaching nerve endings release less transmitter.[11] This mechanism is the basis of presynaptic inhibition. Presynaptic inhibition is common in the nervous system. For instance it is thought to account for the gate-control theory of pain, whereby activation of the GABAergic interneurons from stimulation of non-nociceptive afferents inhibits transmission from nociceptive neurons to projection neurons in the dorsal horn of the spinal cord (accounting for the analgesic action of counter-irritants, such as rubbing an injured area or using methylsalicylate preparations to minimize pain).

How does depolarization of the primary afferents, the PAD, prevent or attenuate the orthodromic transmission of APs to cause pain relief?

Based on studies of crayfish systems, two possible explanations have been offered.[12] One is that the shunting effect of greatly increased Cl- conductance decreases AP amplitude so as to decrease transmitter release. The other is that subthreshold depolarizations result in inactivation of Na+ channels. The depolarization initially activates some Na+ channels, but not enough to reach threshold. These Na+ channels, following activation, quickly inactivate and are then unavailable to open in response to the orthodromic AP coming in from the periphery. The unavailability of some fraction of the Na+ channels means that the inward current associated with the AP is reduced, resulting in a lower amplitude AP. Another possibility is that APs induced by PADs and travelling antidromically collide with incoming nociceptive APs, canceling them out. This raises the question of why APs initiated in the cord by PADs are not perceived as pain. Evidence from the crayfish system indicates that the site of the axo-axonic synapse is not right at the afferent nerve endings, but at least 200 μm distant, and that PAD-initiated APs travel only antidromically and do not reach the endings within the cord. The mechanisms by which this occurs are discussed by Cattart and Clarac.[12]

nerves in the cord, ie, DRRs. PAG stimulation results in GABA release from interneurons in the cord and serotonin release from descending fibers originating from the raphe magnus nucleus of the brain stem. (PAG gray activity stimulates raphe magnus activity.) PAG stimulation has been shown to cause pain modulation, in which transmission of nociceptive inputs is inhibited. There is evidence that both GABA and serotonin play a role in this by causing primary afferent depolarization.[14] The fact that PAG stimulation affects primary afferent depolarization indicates that processes of the central nervous system, which affect PAG output, have the potential to cause or contribute to neurogenic inflammation. PAG output is known to be influenced by higher centers – such as the prefrontal cortex and amygdala – areas that are strongly associated with processing emotion. It is possible that such activity can contribute to localized or generalized inflammatory disorders, thus providing a neural link between emotional states and neurogenic inflammation.

Manipulative treatment inhibits pain transmission in experimentally-induced joint inflammation.

Skyba and colleagues[15] have shown that knee joint manipulation acts in an analgesic manner in rats with experimentally induced arthritis in the ankle joint. This analgesia is blocked by local application of a serotonergic blocking agent, methysergide, to the dorsal horn of the cord. Blockade of adrenergic transmission in the cord with yohimbine (an α2-adrenergic blocker) also interferes with the analgesic effect of joint manipulation. GABAergic blocking agents had no effect, and neither did the opioid antagonist, naloxone. These results suggest that the analgesic effect of joint manipulation acts at the level of the brain stem where the descending serotonergic fibers originate. Serotonin, released from neurons descending from the brain stem to the cord, is known to cause PADs. Thus, joint manipulation appears to provide analgesia by subthreshold PADs caused by serotonin release. This effect may be a direct effect of serotonin released onto primary afferents; serotonin receptors are known to exist on primary afferents in the cord. The effect may also be mediated, at least in part, indirectly by the release of GABA from interneurons, although Skyba's data suggests that such a mechanism is at best secondary.[15] Release of serotonin in the cord is also known to activate interneurons which release opioids, specifically enkephalin,[16] but these appear to play no role in the analgesic effect of manipulation.[17] The serotonergic system is complex, with different receptors that have different, and sometimes opposite effects on primary afferents.[18] Much remains to be learned about this system and its role in pain modulation. Further work will be required to elucidate fully the analgesic pathways activated by joint manipulation and other forms of manual treatment.

What role do the sympathetics play?

Results with the experimental model of arthritis induced in rats by injection of kaolin and carageenan into the knee joint, in which DRR reflexes play a prominent role, suggested that the sympathetic nervous system played little or no role.[19] DRRs

occurred even after sympathectomy or in the presence of adrenergic blockade.

The role of sympathetic activity in SD and in the modulation of pain, however, has been important in osteopathic thinking,[20] and other experimental evidence has suggested a relation between sympathetic activity and somatic dysfunction.[21,22] Using a model of peripheral inflammation induced by injection of capsaicin into the skin of the foot in rats, Lin and colleagues[23] reported that the flare was reduced by previous sympathectomy. Using the same model, Wang and colleagues[24] have shown that the enhancement of DRRs caused by induction of the inflammation is completely prevented by previous sympathectomy or treatment with the α1 adrenergic blocker, terazosin. These results indicate a modulatory role for the sympathetics in neurogenic inflammation, which may vary according to the tissue involved or the specific agents causing the inflammation.

Summary

Direct evidence now exists to support the ideas: (1) that efferent activity can be initiated on sensory (dorsal root) neurons both from central and peripheral inputs and can travel antidromically to generate (neurogenic) inflammation in the periphery; (2) that joint manipulation can reduce hyperalgesia by activating descending serotonergic and adrenergic pain modulating pathways; and (3) that these two processes both involve primary afferent depolarizations in sensory nerve endings of PANs in the spinal cord. Depending on their intensity, primary afferent depolarizations can be nociceptive or anti-nociceptive, ie, promote pain or inhibit pain.

Much remains to be learned about the behavior of primary afferents in response to various inputs, and specifically, their relation to somatic dysfunction. Osteopathic manipulative techniques vary, and simple joint movement, as studied by Sluka and colleagues[19] is no doubt incomplete as a model; but these results from neuroscience may, nevertheless, point to at least some of the mechanisms through which SD occurs and through which osteopathic manipulative treatment relieves pain and restores normal function.

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