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REVIEW

Interactions between the painful disorders and the autonomic nervous system

Otonom sinir sistemi ve ağrılı bozukluklar arasındaki etkileşimler

Doruk ARSLAN,[1] Işın ÜNAL ÇEVİK[2]

Summary

The autonomic nervous system (ANS) controls the heart rate, blood pressure, digestion, respiration, pupillary reactivity, sweating, urination, sexual arousal, and regulates the functions of internal organs. This system provides the homeostasis of the cells, tissues, and organs throughout the body and protects against the disturbances imposed by the external and internal stressors. The ANS has three main divisions: The sympathetic nervous system (SNS), the parasympathetic nervous system (PNS), and the enteric nervous system. In general, the SNS and PNS have opposing effects. Each region belonging to the "pain matrix" interacts with ANS. The descending system regulates pain and creates a regulatory effect by the contribution of aminergic neurotransmitters. Hypothalamus, amygdala, and periaqueductal gray are the main structures of this regulatory system. Dysfunction of the ANS is frequently observed in pain patients. The SNS induce, facilitate, or potentiate chronic pain. Increased responsiveness of injured sensory nerves to catecholamines, increased expression of α-1 adrenoreceptors on the primary afferent nociceptors and hyperalgesic skin, central sensitization rendering Aβ mechanoreceptors, enhanced discharge and sympathetic sprouting in dorsal root ganglia, central sensitization, and dysfunction of the pain modulation is proposed mechanisms. In this review, the anatomical, physiological and pathological aspects of ANS and pain, and laboratory tests to evaluate autonomic functions will be discussed. Pathophysiological role of ANS in migraine, trigeminal autonomic cephalgias, trigeminal neuralgia, peripheral nerve injuries, small fiber neuropathies, myofascial pain syndrome, fibromyalgia, painful joint diseases, visceral pain, phantom limb pain, complex regional pain syndrome, and spinal cord injury will be discussed.

Keywords: Anatomy; mechanism; pain; parasympathetic nervous system; physiology; sympathetic nervous system.

Özet

Otonom sinir sistemi, iç organların fonksiyonlarını düzenler, kalp atım hızını, kan basıncını, sindirimi, solunumu, pupiller reaktiviteyi, terlemeyi, idrara çıkmayı ve cinsel uyarılmayı da kontrol eder. Otonom sinir sistemi vücuttaki hücrelerin, dokuların ve organların homeostazını sağlamaya ve iç/dış zorlayıcı etmenlerin sebep olduğu hasara karşı koymaya çalışır. Otonom sinir sisteminin üç ana dalı vardır: sempatik sinir sistemi, parasempatik sinir sistemi ve enterik sinir sistemi. Genel olarak, sempatik sinir sistemi ve parasempatik sinir sisteminin birbirine zıt etkileri bulunmaktadır. Ağrı matrisine ait her bölge otonom sinir sistemi ile etkileşim içerisindedir. İnen yolakları ağrıyı düzenler, aminerjik nörotransmitterlerin katkısıyla sistem üzerine regülatör bir etki yaratır. Hipotalamus, amigdala ve periakuaduktal gri cevher bu düzenleyici sistemin ana yapılarıdır. Otonom sinir sisteminin işlev bozukluğu ağrılı hastalarında gözlenebilmektedir. Sempatik sinir sistemi, kronik ağrıyı indükleyebilir, kolaylaştırabilir veya güçlendirebilir. Hasarlı duyu sinirlerinin katekolaminlere karşı artmış hassasiyeti, primer aferent nosiseptörler ve hiperaljezik cilt üzerinde alfa-1 adrenoreseptörlerinin ekspresyonunda artış, Aβ mekanoreseptörleri aracılı merkezi sensitizasyon, dorsal kök ganglionlarında artmış deşarj ve sempatik filizlenme, santral sensitizasyon ve ağrı modülasyonunun disfonksiyonu bu sürece katkı sağlayan mekanizmalar olarak sayılabilir. Bu derlemede otonom sinir sistemi ve ağrının, anatomik, fizyolojik, patolojik yönleri ve otonomik fonksiyonları değerlendirmek için kullanılabilecek laboratuvar testleri tartışılacaktır. Otonom sinir sisteminin migren, trigeminal otonomik sefaljiler, trigeminal nevralji, periferik sinir yaralanmaları, ince lif nöropatisi, miyofasiyal ağrı sendromu, fibromiyalji, inflamatuvar eklem hastalıkları, viseral ağrı, fantom ağrısı, kompleks bölgesel ağrı sendromu ve spinal kord hasarındaki patofizyolojik rolü tartışılacaktır.

Anahtar sözcükler: Anatomi; ağrı; fizyoloji; mekanizma; parasempatik sinir sistemi; sempatik sinir sistemi.

[1]Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[2]Department of Neurology, Pain and Headache Unit, Hacettepe University Faculty of Medicine, Ankara, Türkiye

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Correspondence: Dr. Işın Ünal Çevik. Hacettepe Üniversitesi Tıp Faültesi, Nöroloji Anabilim Dalı, Ağrı ve Baş Ağrısı Ünitesi, Ankara, Türkiye.
Phone: +90 - 312 - 305 2585 **e-mail:** isin.unalcevik@gmail.com

Introduction

Pain is a complex sensation. It has sensory - affective, cognitive - evaluative, and motivational components.[1] Many different regions scattered throughout the neuroaxis are involved in pain processing.[2] This review will focus on the autonomic nervous system (ANS) and its interactions with the painful disorders.

ANS

The ANS is necessary for the homeostasis of the body, it coordinates many physiological events such as metabolism, circulation, respiration, body temperature, digestion, sweating, circadian rhythm, immune response, reproduction, and endocrine release. Walter B. Cannon described the ANS as the "wisdom of the body," a neuronal network that provides the neural control of almost all parts of the body except the skeletal muscles.[3] The ANS has three main divisions: The sympathetic nervous system (SNS), the parasympathetic nervous system (PNS), and the enteric nervous system (ENS).[4] In general, the SNS and PNS have opposing effects. The SNS is defined as "the fight or flight," and the PNS as "the rest and digest," while the letter "S" in "Sympathetic" may be linked to "Stress" and organized to mobilize the body for activity. The letter "P" in "Parasympathetic" may be linked to "Peace," which represents the reactions of the body in a state of rest, digestion, diuresis, and defecation.[5] The ability to adapt to environmental stressors is severely challenged by autonomic failure.[6] The ENS functions with the PNS and SNS to control digestion.[7]

The anatomic organization of the ANS

The SNS and PNS outputs consist of preganglionic neurons scattered in the brainstem or spinal cord, and the postganglionic neurons innervate the target organ (Fig. 1). Autonomic outputs are usually phasic responses that occur with latencies specific to neural reflexes.[8]

The cell bodies of sympathetic preganglionic neurons are located in a longitudinal extension of the spinal cord, often limited to thoracic and lumbar segments, the "thoracolumbar part" of the ANS. The PNS is called the "craniosacral part" as the location of its preganglionic neurons are in the midbrain, pons, medulla, and the sacral spinal cord. Both sympathetic and parasympathetic preganglionic myelinated fibers release acetylcholine (Ach). The postganglionic short, unmyelinated parasympathetic fibers, release Ach. The postganglionic long unmyelinated sympathetic fibers release norepinephrine (NE) as at most endings and Ach at few endings (sweat glands) (Fig. 1 and Table 1). In contrast to the limited spinal localization of autonomic neurons, α- and γ-motor neurons, which control skeletal muscles, are distributed along the length of the spinal cord from the cervical to the sacral levels.[9]

SNS

Sympathetic preganglionic neurons are located in the T1 to L2 segments of the thoracolumbar spinal cord. These preganglionic neurons show a selective activity in response to orthostatic stress, temperature change, hypoglycemia, bleeding, exercise, or a particular emotion.[10] NE and epinephrine (E) act through different α1, α2, and adrenoceptor subtypes. α1 adrenergic receptors mediate the stimulation of smooth muscles in blood vessels, iris, vas deferens, bladder neck, and internal sphincter of the rectum. The α2 adrenergic receptors are mostly located at presynaptic terminals and mediates presynaptic inhibition of NE release from sympathetic terminals. The β1 adrenergic receptors are located in the heart and stimulate the automatism of the sinus node, excitability of the His-Purkinje system and contraction of the myocardium. The β2 adrenergic receptors provide vasodilation, bronchodilation, and relaxation of smooth muscles.[9]

PNS

Preganglionic parasympathetic neurons are localized in brainstem cranial nuclei and sacral spinal cord segments S2–S4. The cranial nerve (CN) III provides inputs to the ciliary ganglion, which mediates pupil constriction and accommodation reflexes. The CN VII provides inputs to the pterygopalatine (sphenopalatine) ganglion to reveal lacrimation, and to the submaxillary and submandibular ganglia for salivation. The CN IX innervates the otic ganglion to support parotid gland secretion. The CN X provides preganglionic innervation to the autonomic ganglia in the thorax and abdomen. In addition, vagal preganglionic neurons located in the dorsal motor nucleus of the vagus nerve innervate the ganglia of the cardiac, pulmonary and ENS plexuses, while the nucleus ambiguus neurons have cardiac functions. The sacral

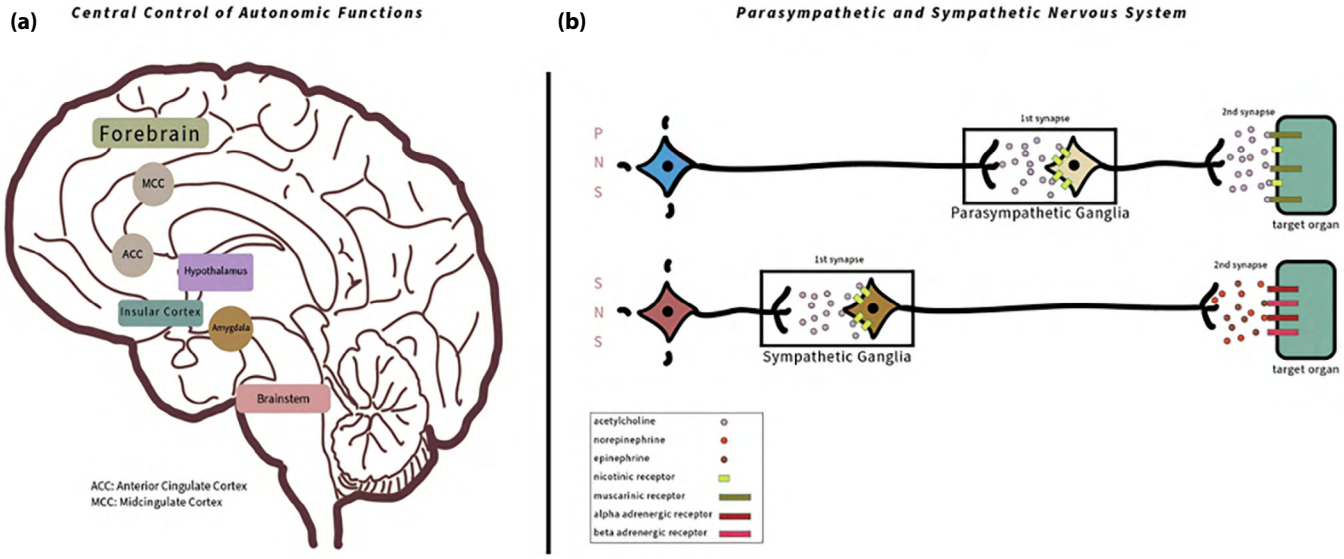

Figure 1. The autonomic nervous system (ANS). **(a)** The central control of the ANS. The central structures which mediate ANS functions are the forebrain, middle cingulate cortex, anterior cingulate cortex, insular cortex, hypothalamus, amygdala, and the brainstem. **(b)** The synapses of the PNS and SNS. The first synapse within the parasympathetic ganglion and the sympathetic ganglia is both cholinergic and releases Ach which interacts with the nicotinic receptors. The second synapse within the PNS is cholinergic and the released Ach from the postganglionic fiber interacts with either muscarinic or nicotinic receptors at the target organ. The second synapse of the SNS is catecholaminergic and the released neurotransmitters are norepinephrine (NE) or epinephrine (E), which act on alpha-adrenergic (mainly NE) or beta-adrenergic receptors (mainly E).

PNS: Parasympathetic nervous system; SNS: Sympathetic nervous system; Ach: Acetylcholine.

preganglionic nucleus is responsible for controlling urination, defecation, and erectile function.[11]

ACh is the primary neurotransmitter of most parasympathetic ganglia and ENS neurons. In target organs, the effects of ACh are primarily mediated by muscarinic receptors, including excitatory M1 and inhibitory M2 receptors. The M3 type mediates the stimulating effects, such as smooth muscle contraction and exocrine gland secretion.[9]

Central control of the autonomic functions

The forebrain and brainstem areas control the activity of preganglionic sympathetic and parasympathetic neurons. This network is involved in the modulation of the functions of the internal organs, maintenance of homeostasis, and adaptation of the body to stressors.[12] Insular cortex, anterior cingulate cortex (ACC), midcingulate cortex, amygdala, and hypothalamus constitute the most important parts of the primary forebrain autonomic areas (Fig. 1). The posterior insular cortex receives and integrates visceral, pain, and temperature sensations. The posterior insula outputs these signals to the anterior insula for the emotional and cognitive processing. The midcingulate cortex mediates the purposeful allocation of effort to control behavior. These cortices play important role in internal perception by broadcasting predictive signals.[12] The amygdala provides affective or emotional value to incoming sensory information.[13] The hypothalamus initiates certain autonomic patterns; it creates endocrine and arousal responses to internal or external stressors.[14] The periaqueductal gray (PAG) in the midbrain coordinates autonomic, somatomotor, and pain regulating responses to stress.[15] The parabrachial nucleus (PBN) in the dorsolateral pons controls cardiovascular, respiratory, and gastrointestinal reflexes.[16]

Autonomic disorders

Dysfunction of the ANS is called "autonomic dysfunction" or "dysautonomia." The generalized autonomic failure due to the damage of both SNS and PNS leads to autonomic hypoactivity. The orthostatic symptoms are associated with cerebral hypoperfusion and dizziness. Common non-orthostatic symptoms include constipation, micturition problems, cold or warm intolerance, excessive or loss of sweating, and erectile dysfunction. The most prominent diffuse autonomic symptoms are fatigue, headache, and insomnia.[4] Dysautonomia can be conceptually divided into three main headings: Orthostatic intolerance syndromes, central dysautonomia, and dysautonomia associated with small fiber neuropathy (SFN). Orthostatic intolerance syndromes are postural tachycardia syndrome, hypocapnic cerebral hypoperfusion, neutrally medi-

Table 1. Anatomic and physiologic characteristics of sympathetic and parasympathetic nervous system

Characteristic features	Sympathetic nervous system	Parasympathetic nervous system
Action	"Fight or flight" response	"Rest and digest" response
Outflow	T1-L2	Cranial nerves III, IV, IX and X; S2-S4
Pre-ganglionic fibers	Myelinated	Myelinated
Ganglia	Paravertebral (sympathetic trunks)	Small ganglia close to viscera (otic, ciliary ganglia)
	Prevertebral (celiac, superior and inferior mesenteric plexus)	Ganglion cells in plexuses (cardiac, pulmonary plexus)
Neurotransmitter within ganglia/ ganglionic receptors	Acetylcholine/nicotinic Acetylcholine receptors (nAChR)	Acetylcholine/nicotinic Acetylcholine receptors (nAChR)
Post-ganglionic fibers	Long and unmyelinated	Short and unmyelinated
Neurotransmitter at post-ganglionic endings	Norepinephrine and epinephrine at most endings and acetylcholine at few endings (sweat glands)	Acetylcholine
End organ receptors	Mainly Adrenergic receptors (α, β) and few Muscarinic Acetylcholine receptors (mAChR) at the sweat glands	Muscarinic Acetylcholine receptors (mAChR) and Nicotinic Acetylcholine receptors (nAChR)
Higher control	Hypothalamus	Hypothalamus

ated syncope, paroxysmal sinus tachycardia, baroreflex failure, and orthostatic hypertension syndrome. Typical disorders of cerebral dysautonomia are multiple system atrophy, Parkinson's disease, and pure autonomic failure. In addition, dysautonomia may be an important reflection of multiple sclerosis. ANS is affected in most of the peripheral neuropathies associated with large fiber loss, but the clinical significance of autonomic dysfunction is very low, except for neuropathies such as diabetes, amyloidosis, Guillain-Barré syndrome, and porphyria.[17] In SFN, both sensory and autonomic fibers are involved; thus, the patients suffer from severe neuropathic pain.

Laboratory tests to evaluate autonomic functions

The screening tests are thyroid function tests, electrocardiogram, ambulatory blood pressure monitoring, transthoracic echocardiogram, exercise stress test, and carotid sinus massage evaluation. The sudomotor axon test, sweat test and sympathetic skin response test, and axon-flare test evaluates peripheral ANS dysfunction. To evaluate autonomic cardiovascular reflexes, Valsalva maneuver or tilt table test are important.[5,18,19] Urodynamic studies are used to evaluate the neurogenic bladder, and gastroenterological tests evaluate the motility functions.[20]

Pain perception and ans interactions

The thinly myelinated Aδ and unmyelinated C fibers transmit the nociceptive stimulus. The nociceptive stimulus rises in the contralateral spinothalamic pathway, it also provides a direct connection to the brainstem through the spinoreticular and spinomesencephalic pathways, and to the hypothalamus through the spinohypothalamic pathway.[21] The neurons located in the dorsal horn project to the nucleus tractus solitarius (NTS) and to PBN, the main integration site for all homeostatic afferent activity. The projections of neurons in the afferent pathway to NTS and PBN clearly reveal the contribution of pain perception to homeostasis.[22] The upper brainstem level of autonomic system integrates autonomic control with pain modulation and behavioral responses to stress. PAG is involved in the coordination of the micturition reflex and the control of respiration. PBN also contributes to the modulation of pain and acts as an autonomous center participating in the control of respiratory, cardiovascular, and gastrointestinal functions.[16]

Each region of the "pain matrix" interacts with ANS.[1] The forebrain level enables the integration of autonomic and pain modulation for homeostasis and adaptation. Anterior limbic areas are involved in in-

tegration of bodily sensation with emotional- and goal-related autonomic responses.[23] The descending pain pathway creates a regulatory tonic effect from the brain to the spinal dorsal root level by the contribution of aminergic transmitters.[21] Hypothalamus, amygdala and PAG are the main regulators. Amygdala is the central nucleus that initiates autonomic, endocrine, and motor outputs critical for the expression of emotional responses.[16] The posterior and lateral hypothalamic areas involved in autonomic control and pain modulation.[23] The PAG receives afferents from the central and peripheral nervous systems and contributes to the modulation of the descending pain pathway. Lateral and dorsolateral PAG initiates flight or fight responses associated with tachycardia, hypertension, and blood flow redistribution.[24] Autonomic arousal is a component of pain response. In experimentally-induced pain models, pain-induced autonomic arousal revealed autonomic reactivity in 39 studies.[25] A relationship between autonomic control of visceral pain and personality traits has been documented.[26] If a person is neurotic or inverted, pain-related autonomic responses may be associated with parasympathetic changes.[26] In patients with somatoform disorders, pain tolerance and autonomic reactivity were found to be different.[27] While sympathetic activity was more prominent, parasympathetic activity was found to be suppressed. The patients with somatoform disorders feel the unpleasant side of the pain more prominently.[27] Sex difference in autonomic modulation of pain has been also been reported.[28] The men with higher parasympathetic activity were reported to have higher efficiency on pain modulation. The females are reported to be more sensitive to pain and less pain reduction in the offset analgesia paradigm due to hormones, psychological factors, and the basal level of parasympathetic activity.[28]

Painful conditions associated with ANS functionality

Headache

Autonomic activation is mainly observed in migraine and trigeminal autonomic cephalalgias. In migraine, the axonal projections of the trigeminal nerve and its vasoactive peptides represent the contribution of autonomic system to headache.[29] The trigeminal fibers originating from the ipsilateral trigeminal ganglion, and sympathetic fibers originating mainly from the ipsilateral superior cervical ganglion, form a dense plexus around the meningeal artery particularly around the dural sinuses. This plexus modulates the vasomotor function.[30] Afferent projections of the trigeminal ganglion receive inputs from adjacent skin, pericranial, and paraspinal muscles. The trigeminal autonomic reflex, the projection between trigeminal sensory afferents, and the superior salivatory nucleus explain the autonomic features in the face. In addition, craniofacial nociceptors may extend to the PBN and this trigeminoparabrachial-limbic pathway processes emotional or motivational aspects of pain.[31] The migraineurs tend to have reduced sympathetic activity during the interictal period, with an increased sympathetic response during the ictal period.[32] HRV is reported to be significantly decreased during the migraine ictal period.[33]

Trigeminal autonomic cephalalgias (TACs) are classified in primary headache disorders that have similar clinical features but differ in frequency and duration. Cluster-type headache is the most common type of TACs, each attack lasting 15–180 min. Other forms of TACs are SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA), Paroxysmal Hemicrania, and Hemicrania Continua. All TACs share an intense unilateral pain in a trigeminal nerve distribution associated with the ipsilateral cranial autonomic features such as lacrimation, conjunctival injection, nasal congestion, and rhinorrhea. The "trigeminovascular system," "trigeminoparasympathetic pathways" involving the superior salivatory nucleus and sphenopalatine ganglion, and predominantly the "hypothalamus" play an important role in the pathogenesis of TACs.[34] During cluster headache attacks, neurogenic vasodilation and trigeminal-parasympathetic discharge can trigger glandular secretions, increase blood flow in the affected area, and induce vasodilation of the intracranial arteries. Once the attack begins, these autonomic disturbances may contribute to a rapid increase of the pain.[35] The attacks are thought to be initiated by the hypothalamic activity.[36]

Trigeminal neuralgia (TN)

TN is a rare neuropathic pain disorder affecting the fifth CN and is characterized by sharp episodes of

paroxysmic pain lasting from a few seconds to minutes. Classical TN is caused by neurovascular compression most frequently by the superior cerebellar artery of the trigeminal nerve roots into the pons. This compression usually results in the demyelination of nerve fibers, which then start firing ectopically. The "ignition hypothesis" was proposed by Devor et al.[37] There is accumulating evidence that voltage-gated sodium channels play a crucial role in the generation of ectopic activity in trigeminal afferents.[38] However, there is also increasing that TN patients may have altered autonomic reactivity to pain.[39] During a TN attack, the TN patients' heart rate variability (HRV) revealed greater increase in cardiac sympathetic activity and greater decrease in cardiac parasympathetic activity, compared to the healthy control.[39] Autonomic symptoms are reported to be present more frequently, if more than one division of the trigeminal nerve were involved. Patients with autonomic symptoms were reported to show lower success rates after surgery.[40]

Smal fiber neuropathies

SFN may be due to hereditary, metabolic, infectious, toxic, immune-mediated diseases, or idiopathic. It mainly affects the small nerve fibers, the myelinated Aδ, and unmyelinated C fibers which are involved in pain transmission and also innervate dermal vessels (vasomotor fibers), sweat glands (sudomotor fibers), and hair follicles (pilomotor fibers).[41] Small fibers consist of small somatic sensory fibers and autonomic C fibers. The clinical symptoms of SFN may be characterized by isolated sensory/autonomic symptoms, such as sweating abnormalities, dry mouth, skin discoloration, and decreased motility of tract.[42] Thermal, electrical, mechanical, or chemical stimulation of dermal nociceptive C-fibers depolarizes small fibers in the skin and creates an antidromic flow response characterized by vasodilation and "flare." The flow properties depend on the amount of activated nerve fibers, and the flow field is thought to be related to the receptor area of the activated C fibers. After the C-fibers are stimulated, neuropeptides such as the calcitonin gene-related peptide generate an "axon-flare response."[43] Quantification of this reflex can be assessed using LASCA method.[44] Recently, we determined the functional properties of small fibers using axon-flare responses in diabetic patients.[45] The LASCA method could potentially facilitate a practical, quick (within 5 min), and very early diagnosis of small fiber hypofunctionality in both patients with impaired glucose tolerance and diabetic neuropathic pain.[45]

Peripheral nerve injury

Peripheral nerve injury may trigger chronic neuropathic pain in selected patients. Histological examinations of the cutaneous nerve fascicle revealed colocalization of nerve fibers and alpha-1 adrenoceptor immunoreactivity in the perineurium.[46] In some patients analgesic response to sympathetic block is observed, as the pain is maintained by active surviving sympathetic fibers.[43] Although the pathophysiology of this sympathetically sustained pain is not fully understood, it appears to be due to abnormal upregulation of α1-adrenergic receptors on nociceptive afferents and the sympathetic deficits evokes supersensitivity to adrenergic agents. In addition, immune proinflammatory mediators play a critical role in the development and maintenance of neuropathic pain.[43] Neurogenic inflammation triggered by α1-adrenergic receptors and injury-evoked inflammation aggravated by keratinocytes, damage the blood-nerve barrier, permits α1-adrenoceptor activation, and leads to nociceptor hyperexcitability, facilitates both pain and axon reflexes, and further aggravate neurogenic inflammation cascade. Thus, the SNS can contribute chronic neuropathic pain through several interrelated mechanisms.[43]

Myofascial pain syndrome (MPS)

Although MPS is the most common musculoskeletal pain disorder, its pathological mechanism is not fully understood. MPS is characterized by palpable trigger points of skeletal muscle that presents pain elsewhere and can cause distant motor and autonomic effects. In MPS, the sympathetic-sensory interaction within a trigger point, may contribute to local and referred pain and sympathetic symptoms. The sympathetic facilitation, mechanical sensitization, and the local and referred muscle pain are reported in MPS.[47] In MPS patients, increased tonic pupillary autonomic activity (sympathetic and parasympathetic), with a relative sympathetic dominance, and decreased tonic parasympathetic cardiovascular activity is reported.[48] In a rat model of MPS, the sympathetic hyperinnervation is also reported.[49]

Fibromyalgia

Fibromyalgia is a chronic widespread painful condition associated with stress. Many studies have tried to investigate how this distress turns into pain. The SNS is the main component of the stress response of the body. Stressors such as physical trauma and infection induce abnormal connections between the SNS and the nociceptive system. The dorsal root ganglia sodium channels may facilitate this type of pain. Genetic factors and/or distressful lifestyle may lead to the state of sympathetic hyperactivity. Patients with fibromyalgia usually have other medical problems such as dry mouth, fatigue, insomnia, anxiety, Raynaud's phenomenon, and irritable bowel syndrome (IBS).[50] In a meta-analytic study evaluating high-frequency HRV in chronic pain patients, decrease in parasympathetic activation predominantly in fibromyalgia patients was reported.[51] Patients with fibromyalgia and IBS show similar pain processing dysfunctions, characterized by reduced descending pain inhibition, accompanied by abnormal autonomic responses (especially in FM patients), a state of sympathetic hyperactivity.[52] Dysautonomia is common in FM, and analysis of HRV characterizes sympathetic hyperactivity.[53] The presence of SFN in many fibromyalgia patients has been demonstrated. This information supports dysautonomia in fibromyalgia patients.[54]

Visceral Pain

The visceral structures (thoracic, abdominal, and pelvic organs) are highly sensitive to distension, stretch, volume, pressure, ischemia, or inflammation. The visceral nociceptive information reaches to the spinal centers by visceral afferents. The visceral afferents are carried by the peripheral nerve that also carries autonomic efferents. The visceral pain is poorly localized and felt more diffuse than somatic pain and often associated with autonomic symptoms. It can even be referred. The "referred pain" is pain perceived at a location other than the site of the painful stimulus/origin. Nerve fibers of higher region sensory inputs such as the skin, and nerve fibers of lower sensory inputs such as the visceral organ, converge at the same level of the spinal cord. This can result in confusion on where the sensation/pain is coming from.[55]

Visceral pain may be related to a wide spectrum of etiology; angina pectoris, peptic ulcer, renal stone, IBS, cystitis and pelvic causes, etc. The contribution of sympathetic activation in visceral pain is important. Adrenergic activation was demonstrated in patients with chronic bladder pain due to interstitial cystitis.[56] Endometriosis is a disorder, in which endometrial tissue grows outside of the uterine cavity. The hormonal changes during the menstrual cycle affect the misplaced endometrial tissue, causing the area to become inflamed and painful. Thus, endometriosis causes chronic pelvic pain characterized by inflammation, which triggers both neurogenesis and angiogenesis and inappropriate autonomic response.[57] In a clinical study to investigate pathophysiology in patients with peritoneal endometriosis, authors reported increased sensory and decreased sympathetic nerve fibers density in peritoneal lesions compared to the healthy control. The authors concluded an imbalance between sympathetic and sensory nerve fibers in peritoneal endometriosis, which might directly be involved in the maintenance of inflammation and pain.[58]

Acute pain is predominantly mediated by the extrinsic afferents from the gastrointestinal tract to the CNS. Extrinsic afferents project to the spinal cord within splanchnic nerves, which contain both extrinsic afferents and sympathetic fibers. Parasympathetic fibers do not normally have a major role in visceral pain transmission, but may be indirectly involved.[59] The vagus nerve and other parasympathetic afferents normally mediate non-painful sensations but can activate brainstem centers responsible for descending inhibition of the peripheral input and therefore dampen pain. The ENS can also be affected by autonomic reflexes, such as paralysis of the gut and associated symptoms.[59] The IBS is the most common gastrointestinal disease, its pathogenesis remains unexplained. The visceral hypersensitivity related to dysfunction of the ANS is proposed. In many studies, increased SNS activity and decreased PNS activity have been implicated in IBS patients.[60,61]

Inflammatory joint diseases (IJD)

Rheumatoid arthritis (RA) and spondyloarthropathies are IJD. A meta-analysis demonstrated that these patients have cardiac parasympathetic autonomic dysfunction and increased risk of cardiovascular events.[62] In an experimental model of arthritis, chronic inflammation of the rat hind paw caused sprouting of autonomics sympathetic fibers into the

upper dermis of the skin. The authors concluded that the transmitters released from the sprouted sympathetic fibers in the synovial membrane and upper dermis contribute to the pain-related behavior, associated with arthritis.[63] Studies in RA patients reported reduced baroreflex sensitivity and HRV, linked to ANS dysfunction and cardiovascular disorders.[64]

Osteoarthritis (OA)

OA is mainly characterized by cartilage degradation, synovitis, subchondral bone sclerosis, and osteophyte formation.[65] The role of ANS in OA patients is reported. Synovium is mainly innervated by the sensory nerves, and the sympathetic nerves. In the early studies of patients with OA, sprouting of sympathetic fibers was reported in the subchondral bone, and the activation was shown to be related with increased bone resorption through β-2 receptors. However, α-7 nicotinic receptor activation on macrophages and chondrocytes was linked to the anti-inflammatory properties.[66] Less data are available on the parasympathetic innervation of joint tissue. Some cholinergic fibers are reported in the periosteum and synovium, these fibers may affect the inflammatory state of the joint, and the vagus nerve is shown to have active anti-inflammatory properties.[67]

Complex regional pain syndrome (CRPS)

CRPS is characterized by local changes in skin temperature, local sweating abnormalities, edema, and changes in nail growth. Subsequent muscle weakness may develop in the affected limb, and even in later stages, the limb cools down, and dystonia may develop. Local inflammation, adrenergic denervation super-sensitivity on the vessels, adrenoceptor upregulation on nociceptors and keratinocytes, auto-antibodies targeting adrenergic and cholinergic receptors, endothelial dysfunction, and reduced cutaneous nerve fiber density contribute to the pain in CRPS. Likewise, accompanying dysfunction of central nervous system, pain modulation and generalized autonomic symptoms such as increased heart rate, decreased HRV, and visceral complaints may contribute the process.[68] To investigate the central component of autonomic symptoms in CRPS, patients with CRPS were compared with stroke patients. Similar patterns of autonomic dysfunction were found in both, with decreased temperature in the affected limb and increased thermoregulatory sweating.[69] While this suggests that the symptoms can be partially explained by central nervous system pathology, the cortical changes in brain regions that control autonomic functions, such as the ventromedial frontal cortex and right anterior part of the insula, also suggested a central origin of autonomic dysfunction in patients with CRPS.[70] Due to the complexity of the mechanisms accompanying the pathogenesis, only 30–50% of the group may benefit from sympathetic nerve blockage.[71]

Phantom limb pain (PLP)

Post-amputation pain affects over 60% of major limb amputees. Dysfunction of the ANS is frequently observed in chronic pain patients. The SNS can induce, facilitate, or potentiate chronic pain. Evidence supporting the role of SNS on post-amputation pain pathophysiology is reported by the increase of pain after epinephrine injection and reduction of pain after sympathetic blockade.[72] Increased responsiveness of injured sensory nerves to catecholamines, increased expression of alpha-1 adrenoreceptors on primary afferent nociceptors and hyperalgesic skin, central sensitization rendering A-beta mechanoreceptors, enhanced discharge, and sympathetic sprouting in dorsal root ganglia is proposed mechanisms.[73] In a study on major limb amputees' refractory to treatment, sympathetic blocks were shown to be effective in PLP (1 h post-injection), but long-term benefits (1 week and 8 weeks) were reported in only a small percentage of patients.[73]

Spinal cord injury (SCI)

In patients with SCI above the sixth thoracic vertebra, reductions in sympathetic cardiovascular control result in hypotension and bradycardia. These abnormalities are the direct reflection of impaired sympathetic circuits in the upper thoracic segments. However, cardiac efferent parasympathetic control originating from the brainstem remains intact. Even if hypotension resolves following SCI, loss of supraspinal control of the SNS below the level of the lesion often results in orthostatic hypotension.[74] In addition to orthostatic hypotension, individuals with SCI may also be affected by sudden bouts of hypertension, known as autonomic dysreflexia (AD), triggered by afferent stimuli below the level of the lesion. This condition is not only characterized by increased arterial blood pressure, but is accompanied by piloerec-

tion above the lesion level, chills, severe headache, paresthesia, and flushing. The incidence of AD in individuals with SCI ranges from 20% to 70%.[75] Besides, below the lesion level, both noxious and non-noxious stimulation can induce a diffuse activation of the SNS characterized by an increase in NE release. The release of catecholamines causes vasoconstriction in most of the vascular territories below the level of injury. Muscle, skin, kidneys, and possibly also the splanchnic territory are affected. Therefore, in contrast to the findings above the lesion segment, pallor and coldness are observed under the lesion segment. Baroreceptor reflex, which is activated by an increase in arterial blood pressure, acts to buffer vasoconstriction by dilation of vascular beds above the level of the lesion and reduction in heart rate. This inappropriate activation of the SNS is associated with AD and occurs several times a day and may even occur asymptomatically.[74,76] The development of both AD and chronic neuropathic pain following high, severe SCI (clinically complete or largely complete), is the prototype of the ANS and pain interaction. Spinal damage and inflammation after SCI induces inflammation and sympathetic sprouting at dorsal root ganglia, by facilitating a sympathetic hyperexcitability and leads to the development of chronic neuropathic pain. On the other hand, loss of descending axons after SCI leads to a decrease in sympathetic tone. The reduction of sympathetic tone forces the upregulation of sympathetic receptors and the reorganization of ANS. Sensitization of sympathetic reflexes by reorganization contributes to AD and systemic immunosuppressive reflexes.[77] Serious SCI will be followed by a long period of recovery phase. During this phase, the sympathetic activity activates various components of the "fight-or-flight" response and lead to persistent pain, which is driven by the continued activity of nociceptors that innervate damaged tissue and proinflammatory cytokines.[77,78]

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