SCIENCE

I will make an effort and write down the most important findings and conclusions of science in the area of functional and pain syndromes in internal organs. I wish as many as possible data to be encompassed, however I am at the same time aware that this is very difficult to perform. Namely, to sum up and write down so many things of such importance (on my hard drive there are over 100.000 pages of medical literature regarding this topic), demands constant and long-term supplementing and adjusting. Concurrently, it would probably be entirely absurd, since already the look at this extensive article would discourage most of the readers from reading. The fact is that etiology (the cause) of chronic pain and functional syndromes of chest, abdomen and pelvis is multifactorial (more different factors), but I will mostly concentrate on mechanism of visceral hypersensitivity (exaggerated sensitivity of inner organs). Exaggerated sensitivity of inner organs is with no doubt the most important pathophysiologic factor (producing symptomatology) with chronic pain and functional syndromes.

Thank you for your understanding.

Chronic pelvic pain syndrome

There can be many causes for chronic pelvic pain. As we exclude obvious and most common organic causes with chronic patient, then it is of course necessary to divert our attention to so-called functional causes, to which hypersensibility belongs. By all means, it is necessary to realise, with different approaches, from which part of the body (intestine, pelvic floor, including its innervation - pudendal nerve, bladder, uterus, musculoskeletal system,..) primary hypersensibility arises, and then try to eliminate it. Very important factor with every chronic pain is a central nerve system including psyche. Re-modulation of a central nerve system too, can maintain and also broaden chronic pain. This hyperexcitability and hypersensibility of central neurones (dorsal horn and supraspinal circuitry) is most often caused by excessive bombarding by periphery.

Since, as already said, all these syndromes are impossible to be scientifically described in a normal scope, I have decided to choose chronic prostatitis and interstitial cystitis/ painful bladder syndrome (chronic pelvic pain syndrome) to describe them in detail, and then finally describe a case of viscero-visceral hyperalgesia together with its mechanisms, since many patients suffer from pain symptoms in more then one inner organ. I will concentrate on mechanisms which are very important with these syndromes and with no exception include nerve system, its remodulation and impacts on not only immune, vascular, muscular (smooth and also skeleton muscles) but also some other systems. All these systems of course affect each other and thus also the nerve system. A very simple example of chronic prostatitis pain is degranulation of mastocytes, which is caused by a substance P (a neuropeptide, produced in spinal ganglion, where nerve cells of sensory neurones are located and is released through nociceptive dendrites into peripheral tissues. Degranulated mastocytes release histamine and serotonin (algogenic substances), which once again stimulate nociceptors and thus cause vicious cycle of pain (a simple example, happening on a peripheral level).

Scientific literature to support the explanation, is listed at the end.

Chronic prostatitis (chronic pelvic pain syndrome)

Chronic prostatitis is a disease of which name suggests inflammation and/or infection of prostate as a cause of chronic pain. Therefore, scientists have extensively researched into direction of infectious etiology of chronic prostatitis, but nowadays in medical community (among chronic prostatitis experts) opinion prevails that infection of any kind is not a cause of problems with 95 % of patients. Many possible theories exist about etiology of chronic prostatitis and most often bacteria was assumed as a cause. Often the assumption was also autoimmune etiology and insufficiencies in glycosaminoglycan layer, which mostly consists of hyaluron and heparin, somatic etiology in a sense of hyperpathic (hypersensitive, hyperspastic, hyperreflexive) somatic muscles of pelvic floor and many other etiologies.

It seems though that we have slowly started to really comprehend and understand, that regardless of etiology, the most important pathophysiologic factor is remodulation and mainly too big an expression of sensoric pain nerve system, where occurs exaggerated sensitivity of elements of nervous system at all levels (nociceptors, splanchnic nerves, prevertebral ganglion, spinal ganglion – DRG, posterior spinal neurones and also supraspinal). Latest findings of neuroscience, mainly in areas of neurophysiology and neurobiology of pain have brought us to wider comprehension of chronic prostatitis, where emphasis is no longer on prostate but on nervous system. Prostate is seen as a terminal organ, where changes and pain are presented due to neuropathology. When we start to understand this model, it quickly becomes clear why patients with chronic prostatitis/chronic pelvic pain syndrome often have also plenty of other problems, such as lower back pain, pelvic floor pain, various problems with defecation and descending colon, pain with interstitial cystitis during menstruation (impact of hormones on transmission of pain), pain in groin etc. Therefore we shouldn't be surprised by the fact that for chronic prostatitis a diagnosis of chronic pelvic pain syndrome (CPPS) has lately been used, even though personally I agree with experts, who use a term pelvic neuropathic hypersensitivity, which, in my opinion, describes the condition even better. This model explains how with chronic prostatitis peripheral and central sensitisation happens and these are the most important pathophysiologic factors, which lead to chronification and also maintain and expand chronic symptomatology. This is the reason that biomedical model

of treatment, which concentrates on an organ, which symptomatology arises from, in our case prostate with chronic prostatitis or bladder with interstitial cystitis, gives no result and has been unsuccessful with vast majority of chronic patients. This model was used through all the previous century and unfortunately additional time will probably pass by, before basic science, which I have studied so eagerly and persistently for more then a decade due to my own symptomatology, reach out to a wide clinical profession, even though best experts of the world, I cooperated and still cooperate with, are perfectly aware of this and are already implementing it in treatment of patients. One of such experts is certainly Professor Jerome M. Weiss from San Francisco, who I cooperated with enormously and was also treated by him. So, multidisciplinary approach (biopsychosocial model), which encompasses also a very important pathology of nervous system (pain as a disease), pathology of all drivers of sensitization process, such as hyperpathic muscles of pelvic floor – somatic drivers, pathology of immune system, such as degranulation of mastocytes, emotional factors....is most likely the only one to have a possibility of positive modulation and improvement of pathology and thus of syndrome of chronic prostatitis/interstitial cystitis (CPPS).

Entire viscera is doubly innervated and so is prostate. It is innervated by parasympathetic (pelvic splanchnic nerves) and sympathetic (thoracolumbal splanchnic nerves) of motor nervous system (efferent). On the same path also sensoric nerves pass (afferent), this is why they are called splanchnic. With chronic prostatitis mostly sacral part of the spinal cord is activated through pelvic splanchnic nerves, but also thoracolumbal part through hypogastric, sacral splanchnic nerves and lumbar splanchnic nerves. The difference is above all in modality of stimulation. When it comes to sensitization and hyperexcitability in nociceptors of prostate, on the level of pelvic plexus or on the level of spinal ganglion (DRG), we talk about peripheral sensitization. Clinically, it also comes to sensitization of spinal dorsal neurones and various ascending spinal pathways (spinothalamic tract …) as well as supraspinal centres for pain, such as anterior cingulate cortex, and this is called central sensitisation.

I have spoken to Professor Clifford Woolf several times (neuroscientist – discoverer of central sensitization phenomena) from Harvard University in Boston (USA) about the importance and impressiveness of central neuroplasticity with chronic visceral pain syndromes. It was very interesting to discuss with him how neuroscientists, only 20 years ago, comprehended central nervous system as a totally non-plastic organ, speaking of pain. Professor Woolf was the first to show how central neurones, due to peripheral damaging input that is too big, change reactivity, also permanently, therefore also how brains are plastic (neuroplasticity) and how this neuroplastitcity is important speaking of chronic pain syndrome.

Peripheral sensitisation of visceral pain syndrome

Peripheral sensitization means too big sensitivity of nervous system, such as nociceptors. Peripheral sensitization is one of pathophysiological factors of chronic pain symptomatic. The cause of its emergence can be some peripheral insult, such as infection, ischemia, injury etc., which cause tissue injury, where certain mediators, which sensitize nociceptors and thus the whole neuro axis, are released. The problem is that these mediators (algogenic substances), which are released from different systems, such as vascular (endothelial derived factors), immune, muscular, nervous etc. can bring to excessive expression of certain receptors on nociceptors, such as neurokinine receptors NK1, which bind substance P, now making the nociceptor more sensitive even to physiological stimulus. Therefore, pain maintains itself per se (pain as a disease) due to hypersensitivity of nociceptors, which additionally stimulate spinal ganglia (DRG – cell bodies of sensory neurones), where amongst others neuropeptides are synthetisized, such as substance P and a calcitonin gene related peptide (CGRP), which is then through nociceptive dendrites released into surrounding tissues, where they additionally cause inflammation (neurogenic inflammation) through vasodilation and extravasation of plasma proteins and stimulation of immune cells for example, since also endothelial cells in a vascular system have for example receptors NKA (a receptor for neurokinin A– »a pain neuropeptide«) or mastocytes have for example receptors NK1. In this process a lot of proinflammatory substances are released (proinflammatory soup – neuropeptides, cytokines....), which have different effects on sensitization of nociceptors and whole neuro axis and also on a vicious cycle of pain.

Central sensitization of visceral pain syndrome

Central sensitization means too sensitive central posterior neurones (dorsal horn neurones) and supraspinal neurones to certain stimulants. This phenomena most often occurs after a chronic damaging stimulation by a peripheral nerve fibres. Sensitivity of posterior neurones during harmful peripheral afferent stimulation depends on more factors, such as local excitatory and inhibitory mechanisms (activation of NMDA, release of GABA) and on descendent influences. On a level of posterior neurones in a spinal cord there begins hypersecretion of certain mediators, such as glutamate (the main excitatory neurotransmitter in a central nervous system) or even hyperexpression of NMDA and AMPA receptors, which are receptors for glutamate. With chronic pain the balance between excitatory and inhibitory local and descendent mechanisms is disturbed into direction of hypersensitivity, in the worst case leading to the degeneration of interneuronic inhibitory neurones (GABA) due to hyperrush of glutamate and also to contraction of descendent inhibition (GABA, serotonin, norepinephrine).

This is central sensitisation, sensory neurones now overreact to physiological and even subphysiological stimulation of any kind. This conditions in a central nervous system (dorsal horn – increase of synaptic power, silent synapsis – ineffective synapsis become effective and expand hypersensitivity – transferred pain..), which can bring to permanent hyperexcitability through activation of protein kinase and induce changes in genes and also changes in periphery (peripheral sensitization), cause chronic pain symptoms. One of the signs of such a process is a deep muscle somatic hyperalgesia or allodynia or even hyperalgesia on skin in lumbosacral myotomes and dermatomes with visceral pain syndromes, such as chronic prostatitis. An example is also a lower level of activation of viscerosomatic motor reflex, which is shown with patients with hypersensitivity syndrome of irritable bowel. With chronic prostatitis we can talk about primary hyperalgesia, being a result of peripheral sensitization and about secondary hyperalgesia (other parts of the body, which share innervation from same spinal segments – viscerosomatic posterior neurones...), being a result of central sensitization.

A transfer of signal on a primary afferent level depends on activation of receptors on a membrane of a sensory nerve. Receptors are generally divided to ionotropic and metabotropic. Ionotropic are ionic channels at the same time and open after binding a certain neurotransmitter. Metabotropic receptors are linked to a secondary G-protein, meaning that after a binding of neurotransmitter, a G-protein spreads and causes opening of ionic channels or a synthesis of secondary neurotransmitter. The most significant receptors, which are important with visceral nociceptive transmission, are described next.

TRVP1 is a vanilloid receptor, which is activated by capsaicin, heat, protones and endovanilloids, such as anandamide, which is produced at high temperature. This receptor is well expressed in urinary tract. Even though it is expressed also in urothelial cells and probably in some others too, I bare in mind here above all hyperexpression on sensory neurones. It was shown that this receptor is hyperexpressed at chronic prostatitis with main symptom of pain, but it is clear that hyperexpression of this receptor is connected also to hyperexcitation of reflex contraction of urinary bladder (detrusor overactivity), most likely through direct excitation of sensory fibres or even through release of neuromediators, which further effect epithelial cells. With syndrome "urgency/ frequency", which can be a classical sign of interstitial cystitis/syndrome of painful bladder, there was shown a hyperexpression of TRVP1 in trigone and this is called a sensory urgency. Purinergic receptors, especially P2X3 receptor, which is specific for nociception, bind adenosine triphosphate (ATP). ATP is released from many different tissues always when a tissue is injured in any way, for example an inflammation. This is chemoexcitation and it was shown that with chronic prostatitis for example, a higher expression of these receptors is established also on a DRG level and thus causes chronic prostatitis pain. Something interesting should be mentioned here too. Purinergic receptors, especially P2X4, are expressed on glial cells in a central nervous system. Glial cells with production of different proinflammatory cytokines, which can sensitize neurones, are a subject of latest, very extensive research as a possible driver of a central sensitisation with chronic pain syndromes.

Important are also receptors, such as 5-HT, which are receptors for serotonin, NMDA receptors, of which main linking neurotransmitter is glutamate (main excitatory neurotransmitter of a central nervous system) and also ASIC's, which mainly react to tissue ischemia, hypoxia and acidosis, prostaglandin receptors, opioid, neurokinin receptors, especially NK1 and others.

I think it is the best that I present my case, explain pathophysiology and also describe the importance of somatic factors, such as myofascial trigger points, osteoligamentous dysfunctions, pudendal neuralgia or neuropathy (so called somatic dysfunctions) of a chronic prostatitis/CPPS.

Symptoms of my chronic prostatitis and pain syndrome of bladder were expressed as a chronic suprapubic pain, as a chronic inability to start urinating with a very weak urine flow, and later also as a severe, progressive pain during bladder filling (syndrome of painful bladder/interstitial cystitis). Pain was severe and I emptied my bladder at approximately 50-100 ml, sometimes even less (normally from 350 to 550 ml). Always when the pain suprapubically was expressed to a higher degree, it was even more difficult to urinate and the urine flow was even weaker. I could urinate only with the help of a bigger intra-abdominal pressure (straining) and no longer spontaneously. Always when the symptoms were expressed to a higher degree, I had also pain bilaterally inguinal, sudden creeps all over the skin of my both calves (signs of central changes), very unpleasant lower back pain and many others, such as reflex spasms in somatic muscles of a pelvis floor. At the same time there was an increased, very annoying pressure in splenic flexion of colon and later also in hepatic flexion (signs of viscero-visceral hyperalgesia – more on this later on). Not to mention the frustration for not being understood by the medical profession and their inability to understand and interpret the symptoms.

My chronic pelvic pain syndrome best fits into a group, where CPPS is induced due to different etiologic factors such as restraining the urge to defecate, restraining the urge to urinate, life with too much sitting, too much cycling with inappropriate seat etc. In this case we can of course think of hyperpathic somatic muscles of a pelvic floor, which can of course also be the cause of CPPS (more on this later on), but I bare in mind CPPS, where due to already mentioned predisposing factors we induce prostatic hypoperfusion, which also influences prostatic nerves, either through direct mechanic compressive injury or due to ischemic/reperfusion (IR) injury of nerves. Too much of sitting or cycling for example, causes significant perineal compression forces while prostate has already basally low

blood flow, and above all it was shown that prostate and prostatic urethra are more sensitive to ischemic/reperfusion injuries as bladder, for example. So, once the nerves are injured due to direct compression factors or due to IR-injuries, the process of nociception starts. After a certain time of sensitization process, peripheral and central sensitization arises, since changes on periphery constantly bombard posterior neurones in a spinal cord, and certainly changes start supraspinally too, certain systems start activating chronically, such as diffuse nociceptive inhibitory system (this can be, for example, a reason why patients with visceral pain are sometimes generally hyposensitive to somatic stimulation – DNIC has a diffuse effect on spinal cord). Therefore, when the process is established, it happens by itself and maintains by itself. This is pain as a disease. On a peripheral level we can find hyperalgesic clinical signs, which are shown with increased pain upon touch of prostate, prostate can be reddened, which can be indicative of neurogenic inflammation, which is a result of excessive release of neuropeptides, being released through nociceptive dendrites into periphery. It is mainly substance P, which activates degranulation of mastocytes and a calcitonin gene related peptide, which along with substance P induce also changes in vascular endothelial cells. The result is leakage of inflammatory and vasodilatory chemicals, such as serotonin, histamine, bradykinin, VIP.... (algogenic substances), which cause edema and even increase transmission of pain signals from periphery. Such a view can show also hyperalgesia and allodynia in surrounding structures, also somatic ones, and is a sign of changes, which happen in a central nervous system.

Now this peripheral hyperalgesia on a level of prostate, bladder neck and internal urethral sphincter can, beside pain, cause also problems with bladder emptying through more mechanisms. Let me name the most important three. Firstly, this hyperalgesia can induce hyperspasticity and hyperreflexivity of internal urethral sphincter and bring to obstructed urination. This was very well described by dr. Dirk Henrik Zermman, speaking of urethral hyperpathia. Obstructed urination can chronically bring to increase of pressure in bladder and also to decompensation of bladder with subsequently worse contractile function. I will not go into a cascade of events which follow, but let me tell you that studies have shown that a common mechanism of decompensation of bladder and of worse contractility with chronic partial outlet obstruction, is ischemia on the level of detrusor smooth muscle. It is interesting that ischemia and hypoxia are also a characteristic how bladders of patients with interstitial cystitis/syndrome of painful bladder react to distention and that pain in some patients is connected exactly to this, as positive influence on pain, at for example hydrodistention therapy correlates precisely with improvement of blood flow. And the third, little less known mechanism, yet very important, is the one where increased chronic pain signals induce reflexive inhibition of bladder contraction in sacral spinal cord (one of the proofs is a therapy with application of botulinum toxin type A into IUS and prostatic urethra, which is amongst others used for functional obstructive urinary retention or for chronic prostatitis with a weak urine flow, and many patients describe improvement of urine flow already before the spasticity of IUS is reduced). It is about botulinum toxin type A, having in addition to a known anticholinergic effect (it inhibits the release of acetylcholine on the level of neuromuscular junction) also a proven antinociceptive effect, when it blocks, for example, release of substance P, which happens already before chemodenervation and reduction of muscular tone. Similar influence to functional obstructive urinary retention with a weak urine flow is assumed also for sacral neuromodulation, where electric stimulation of big myelinated nerve fibres brings to inhibition of transmission through unmyelinated C nociceptive fibres. So, a reduction of nociceptive transmission from IUS brings to improvement of contractility of smooth detrusor muscle through sacral spinal cord. Of course a sacral neuromodulation can also have an effect on other CPPS through different mechanisms and of course botulinum toxin type A is also used for other urinary pain syndromes, such as interstitial cystitis, where it is injected to different parts intravesically.

Let me now also mention muscles of pelvic floor, which can also be, as already said, an important factor in generating CPPS symptomatics. When we deal with a patient, diagnosed with either too big tone or hypersensitivity or inability of conscious contraction and relaxation of pelvic floor muscles, our attention must focus also on these important, possibly even etiologic factors of chronic pain syndrome. There are more causes to these findings and range from osteoligamentous dysfunctions, myofascial dysfunctions including trigger points to pudendal neuralgias and neuropathies, emotional and mental causes, such as childhood elimination syndrome and also to presence of primary hyperalgesia in viscera (for example interstitial cystitis). Of course I talk about causes, which are not connected to any of severe organic illnesses, such as multiple sclerosis or a syndrome of cauda equina, which can bring to disturbances in neurologic reflexes, which command urinary tract etc. I again decided to choose one of above mentioned and describe it in detail.

Myofascial trigger points

Myofascial trigger point is a spot of excessive irritation on a muscle or muscular layer. A trigger point can be in an active or static state and it arises due to different causes, such as long-term forced position of muscles, injury, stress etc. Since we talk about trigger points which arise in muscles of pelvic floor, a cause can also be excessive urge to defecate suppression or urine suppression and different injuries of lumbo-pelvic-hip complex, which bring to structural imbalances in osteoligamentous and myofascial structures. Of course a cause can also be primary pain syndrome in viscera (interstitial cystitis, chronic prostatitis…), which due to hypersensitivity of central posterior neurones causes excessive reflexive contraction in somatic muscles, innervated with pudendal nervous system (lowered threshold of viscerosomatic reflex activation). Best hypothesis of trigger point formation is execution of

eccentric contraction of untrained muscle or, of course also execution of maximal or submaximal concentric contraction. This behaviour leads to micro injuries in muscles and to segmental hypercontraction within muscle fibres. Extra physical stress due to muscle hypercontraction is caused also by capillary constriction and muscle hypoperfusion, which is additionally stimulated by excessive activation of adrenergic sympathetic tone. Result of this are ischemia and hypoxia, which, apart from accelerating tissue injury of muscle fibres, also cause a decrease of Ph value in micro environment. It has been shown that a decrease in Ph level causes inhibition of acetylcholinesterase activities (which cause worse decomposition of acetylcholine and consequently maintain hypercontraction), causes increased release of a calcitonin gene related peptide, and of course activation of receptors, such as TRPV1 and ASIC on muscle nociceptors. If I previously spoke about CGRP as of a neuropeptide, which is produced in spinal ganglia and is through nociceptive dendrites released into peripheral tissues and is included in processes of sensory neurotransmission, I talk about an extra function of CGRP here, which due to a simultaneous release with acetylcholine at a synaptic end of a motor nerve (pre synapse) causes accelerated release of acetylcholine into a neuromuscular junction (synapse) and accelerates motor effects (muscle contraction) and causes also an increased expression of acetylcholine receptors on a membrane of muscle fibres. Already a low Ph in a micro environment is a sufficient factor, which can induce changes in sensitivity not only of peripheral but also of central neurones. However, micro injuries of muscle fibres also appear, from where different proinflammatory mediators are released, such as substance P, CGRP, serotonin, bradykinin, prostaglandin and others (increased concentration of these substances in microenvironment of a trigger point is shown in a study, where content was measured with microdialysis), which results in alteration of activities of neuromuscular junction and also of muscle nociceptors with final phenomena of peripheral and central sensitization. Neuroplastic changes on a level of posterior central neurones (central sensitization, silent synapses become active....) which emerge due to chronic nociceptive bombarding from a trigger point, cause allodynia and transferred pain (possibly also in viscero-viscerosomatic central neurones – a neurone which reacts to a somatic and also to visceral stimulation) which are so typical of a trigger point. A local twitch and allodynia on a level of a trigger point (local twitch response), which is also a very important characteristic, are most likely a reflection of changes in spinal cord, where excitability is drastically increased and sensitization emerges. As an interesting fact I can tell (I will not go into detail) that different treatments of trigger points, such as ischemic compression or even better dry needling, lead to a decrease of algogenic substances concentration in micro environment of a trigger point (shown with micro dialysis method), yet it is necessary to tempt a local twitch response (LTR).

Viscero-visceral hyperalgesia

As already mentioned, I will also briefly touch mechanisms which are expected for viscero-visceral hyperalgesic syndromes. There are many patients, who describe pain symptoms, related to more than one inner organ. For example, many patients with chronic prostatitis or interstitial cystitis also have an irritable bladder syndrome. It has been shown that these syndromes (pain in more organs concurrently) are predominantly a result of nervous system reflexes. So, with the use of intravesical application of capsaicin in neurotoxic level (desensitization of sensory neurone through TRPV1) a hypersensitive bladder in patients with induced hyperalgesia in a descending colon was eliminated. Many patients with a hypersensitive esophagus describe symptoms in other parts of gastrointestinal tract etc. Many women with interstitial cystitis, irritable bowel describe symptoms in line with dysmenorrhea, which is indicative also of importance of female hormones influence on pain transmission and symptomatology of CPPS. Still, these hormones play a different role in a patient with CPPS then in a healthy woman, since the sensitivity of a nervous and an immune (for example mastocytes) system to estrogens is changed. These viscero-visceral hyperalgesic syndromes are mostly developed slowly and after a certain period a patient realises that a disease must have progressed (which, together with no understanding of medical profession and diagnostics with no or only minimal findings makes him extremely frustrated), even though it is in fact most likely about chronification of pain as disease, at which extra symptoms are created due to chronic changes in a nervous system, predominantly in a central but also in a peripheral one.

I will concentrate on pelvic viscero-visceral hyperalgesia (pelvic organ crosstalk). Three main mechanisms are anticipated, which lead to such syndromes and issues. Also female hormones play an important role at neuromodulation. First mechanism of viscero-visceral hyperalgesia describes a possibility of a hyperalgesia transfer from one organ to another through spinal ganglia neurones. When there is a primary hyperalgesia in, for example, descending colon (irritable bowel syndromes) a propagation of damaging signals from periphery to spinal ganglia causes hyperexcitability of their neurones. When these same neurones in DRG have axon links to a neurone from other visceral structures (for example bladder – convergent neurone), then antidromic stimulation can cause a release of neuropeptides in this secondary organ (bladder). This of course activates familiar cascade of events (neurogenic inflammation) with influence to a vascular and immune system, such as vasodilation, extravasation of plasma with a release of proinflammatory substances and as a final result a peripheral sensitisation (pain and dysfunction) in a secondary organ.

The other mechanism of viscero-visceral hyperalgesia and a transfer of hyperalgesia from one organ to another predicts a posterior spinal cord where central sensory

neurones (dorsal horn neurones) are located. Sensory inputs from hyperalgesic organ and sensory nerves from normosensitive organ with no pain and dysfunction can be attached to same spinal interneurones in posterior spinal cord. These are viscero-visceral convergent sensory neurones and it is a fact that on a level of lumbosacral and thoracolumbal neurones also viscero-visceral ones were found.

Third mechanism of convergence includes also supraspinal mechanisms, where there are also centres for modulation of reflex coordination, which are important for normal activity of inner organs. Neurone axons in a posterior spinal cord, which get afferent information from pelvic organs, project to brain stem (importance of a spinothalamic tract with pain) and hypothalamus. A descendent reaction to a hyperalgesic input from a peripheral organ also have an influence to intensity, persistence and expansion of pain, which is connected also to our experience, etc. Therefore stress, fear and other emotional factors, which arise due to peripheral visceral hyperalgesia, modulate experiencing of pain. This is the reason that countless times patients are confused, when they realise, that also ‘'psychical condition" is very important, because they finally think exactly what doctors suggest to them, which is a psyche being a cause of all problems. Unfortunately they also realise that with only psychiatrical procedures they will not be able to eliminate the disease and again they are overwhelmed by a very unpleasant feeling that something must be wrong in a physical sense. So, explanation of this is, that supraspinal factors, to which also "psyche" belongs, only modulate symptomatics.

These three levels in a hierarchy of a nervous system, usually in combination, coordinate and modulate pelvic viscero-visceral hyperalgesia.

The impact of female hormones on transmission of pain and on more frequent viscero-visceral hyperalgesia with women

Apart from many different impacts and roles of female sex hormones (estrogen, progesterone), which different specialists know very well, I concentrate on an impact of these hormones to a transmission of pain, which is crucial with chronic pelvic pain syndrome. It has been shown that estrogen receptors are widely expressed not only in a peripheral but also in a central nervous system. It has been shown that, for example, with a patient with estrogen deficiency, treatment with estrogens improves symptomatics of urge incontinence. Cyclic hormonal fluctuations have a great impact on an expression of CPPS symptoms. Many patients with interstitial cystitis also have an irritable bowel syndrome and it often comes to exacerbation of symptomatics perimenstrually. Many patients with an irritable bowel syndrome are also diagnosed with dysmenorrhea. Dysmenorrhea (unusual painful menstruation) is one of the most common causes of CPPS with women in a fertile period. Scientists have studied modulatory impacts of pathologies of female reproductive system (asymptomatic endometriosis, dysmenorrhea, benign cysts on ovaries) on hyperalgesia, which comes from urinary tract (viscero-visceral hyperalgesia). They have realised that patients with dysmenorrhea and urethral stones, feel pelvic pain predominantly perimenstrually and in an ovulation period, whereas patients without dysmenorrhea but with urethral colic, due to stones feel the pain throughout the cycle, exacerbating perimenstrually. This is indicative of an important role of estrogens in a modulation of viscero-visceral hyperalgesia. It has been shown, for example, that female hormones have no fundamental impact on pain with physiologic happening in pelvis, whereas an impact becomes obvious, when there is one hyperalgesic organ or more. Thus, for example, physiologic concentration of estradiol accelerates release of histamine from mastocytes under stimulation of substance P. Not only substance P but also histamine causes vasodilation and hereby neurogenic pelvic inflammation.

I explained some science of chronic pelvic pain syndromes (chronic prostatitis and interstitial cystitis). I also explained the importance of mechanisms of viscero-visceral hyperalgesia and female sex hormones with their neuromodulation.

Rok Ljubič

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