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REVIEW

Visceral pain originating from the upper urinary tract

Katja Venborg Pedersen · Asbjørn Mohr Drewes · Poul Christian Frimodt-Møller · Palle Jørn Sloth Osther

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Abstract Pain originating from the upper urinary tract is a common problem and stone colic is one of the most intense pain conditions that can be experienced in the clinic. The pain is difficult to alleviate and often leads to medical attention. In humans, pain mechanisms of the upper urinary tract pain are still poorly understood, which often leads to a trial and error approach in clinical pain management. Pain from the upper urinary tract seems to have all the characteristics of pure visceral pain, including referred pain with or without hyperalgesia/trophic changes in somatic tissues and viscero-visceral hyperalgesia. However, further studies are needed to better understand these visceral pain mechanisms with regard to optimising pain management. This review gives an introduction to visceral pain in general and upper urinary tract pain in particular, with special reference to pain pathways and pharmacological and non-pharmacological pain modulation.

Keywords Urinary tract · Pain · Renal colic · Renal stone

K. V. Pedersen · P. C. Frimodt-Møller · P. J. S. Osther (✉)
Department of Urology, Hospital Littlebelt,
University of Southern Denmark,
Dronningensgade 97, 7000 Fredericia, Denmark
e-mail: palle.joern.osther@slb.regionsyddanmark.dk

K. V. Pedersen
e-mail: katja.venborg@slb.regionsyddanmark.dk

A. M. Drewes
Mech-Sense, Department of Gastroenterology,
Aalborg Hospital, Aarhus University Hospital,
Mølleparkvej, 9000 Aalborg, Denmark

Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]. According to origin, pain may be divided into visceral, somatic or neuropathic pain. Visceral pain is complex and one of the most frequent reasons for patients to seek medical attention [2]. In the upper urinary tract, pain is also a common problem, e.g. a prevalence of 10% of urolithiasis in Western Europe [3]. It is a clinical experience that "stone colic" is one of the most intense pains that can be experienced. It is difficult to alleviate and often leads to hospitalisation and sometimes surgical intervention. The pathogenesis behind symptoms in urolithiasis is poorly understood and frequently there is a mismatch between disease severity (e.g. stone size) and symptoms. Despite this, there has been a lack of research in this field. In recent years, however, research has been directed towards visceral pain mechanisms in general and as there is a major overlap between pathogenesis in different visceral diseases, this has shed light on pain originating from the urinary tract.

The aim of this article was to review the pathophysiology behind the pain originating from upper urinary tract. We searched Pubmed, Embase and Web of Science using the keywords "visceral pain and urinary tract", and found 111, 58 and 172 references, respectively. Only the studies concerning pain in the upper urinary tract were included in the review and therefore bladder pain and the impact of obstruction on renal hemodynamics, renal function and renal reflexes are not discussed. The review is divided into (1) visceral pain mechanisms in general and (2) pain mechanisms related to the upper urinary tract.

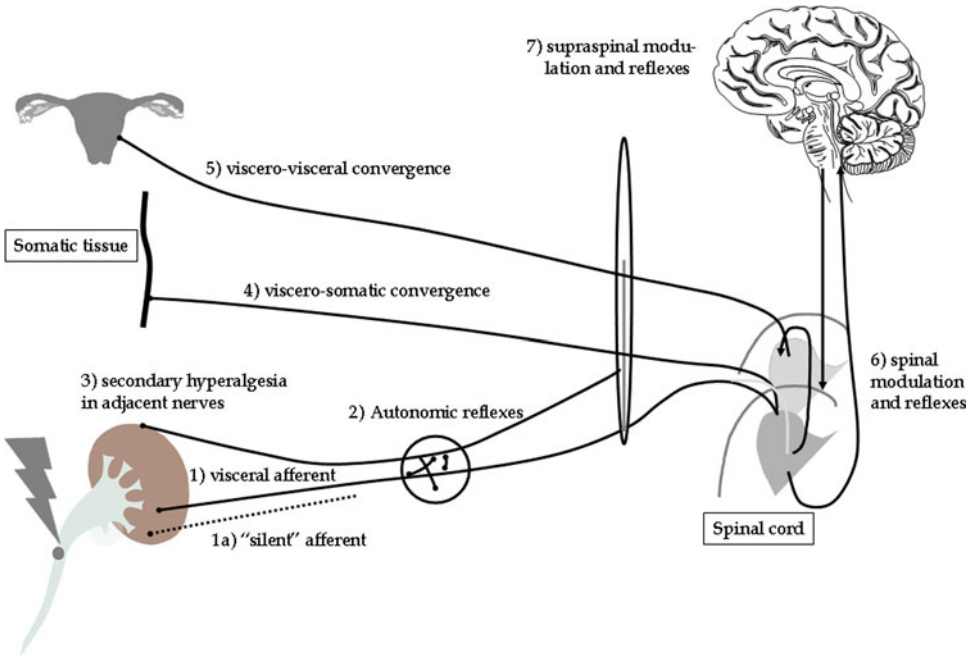

Fig. 1 The multiple nervous pathways involved in visceral pain. Visceral nociceptive stimuli can lead to action potentials in true visceral afferent (*1*), or the inflammation can activate "silent" afferents (*1a*) that are not normally active. Autonomic reflexes (*2*) will typically contribute to the pain. Ongoing stimulation can sensitise the nerves and lead to secondary hyperalgesia (*3*). Viscero-somatic (*4*) and viscero-visceral (*5*) convergence between neurons at the spinal cord may give referred pain and visceral allodynia in areas remote from the original lesion. Finally, spinal (*6*) and supraspinal (*7*) modulation and hyperexcitability may influence the pain and discomfort experienced by the patient

Visceral pain mechanisms in general

Visceral versus somatic pain

Visceral pain differs from somatic pain in several ways:

1. Pain is not evoked from all viscera (e.g. liver-, lung-, and kidney parenchyma are not sensitive to pain). The explanation of this relates to the functional properties of the peripheral receptors in different visceral organs and the fact that many visceral organs are innervated by receptors whose activation does not reach consciousness [2, 4].
2. Visceral pain is not necessarily linked to injury (e.g. cutting the ureter is not painful). Effective visceral stimuli producing pain includes distension, ischemia and inflammation and likely a combination of stimuli are necessary to evoke pain [2, 4].
3. Pain is diffuse and poorly localised. This is explained by the few sensory visceral afferents relative to the afferent innervations of somatic tissues. Furthermore, the visceral afferents terminate diffusely in the spinal cord and have extensive divergence on the 2nd order neurons [2, 4]. For example, in the thoracic spinal cord, more that 75% of all neurons receive both somatic and visceral information. This is contrasted by the actual number of visceral afferents (5–15% of the inflow) entering the dorsal roots [5]. The clinical presentation of the visceral pain can, however, change over time. If inflammation, e.g. appendicitis, becomes transmural, somatic-like afferents in the peritoneum are involved and the pain becomes localised [5].
4. Pain is referred to the body wall because of somatic (skin, muscle, etc.) and visceral afferents terminating on the same dorsal horn neurons in the spinal cord (viscera-somatic convergence). Due to reflex mechanisms, the area of referred pain may exhibit secondary hyperalgesia, muscle tension [2, 4] and trophic changes [6].
5. Pain is accompanied by motor- and autonomic reflexes, e.g. in renal colic nausea and vomiting. Absence of a separate visceral sensory pathway explains this [2, 4]. Hence, visceral afferents travel together with afferents of the autonomic nervous system, with rich possibility for crosstalk between the nerves at local and central levels [5].

The nervous pathways involved in visceral pain are summarised in Fig. 1.

Physiology of the visceral pain system

Basically, the pain system consists of afferent peripheral fibres (1st order neuron), which in the spinal dorsal horn transmits the information to the 2nd order neuron. This neuron transmits the information to the brain (3rd order

neuron), where the information is distributed to different supraspinal centres for processing. In addition, there is a descending control system from the brain that modulates the incoming signals to the spinal cord.

Peripheral afferents

Visceral afferent fibres are either thinly myelinated Aδ-fibres (approximately 20%) or unmyelinated C-fibres [7]. Visceral fibres have free nerve endings, in the literature generally referred to as nociceptors. These nociceptors are polymodal in character, i.e. they respond to mechanical, thermal and chemical stimulation [5]. Activation of the nociceptors result in graded responses giving noxious signals that reflect the stimulus' intensity [5]. The afferent fibres terminate in the spinal dorsal horn mostly in laminae I and V [2]. Most second-order spinothalamic cells in lamina I are nociceptive specific cells, whereas those in lamina V mainly are "wide-dynamic neurons" having graded responses to physiologic as well as noxious stimuli [8].

The visceral afferents converge on a large scale with neurons in lamina I and V that receive input from superficial and deep somatic tissue as well as other viscera [9]. This convergence manifest clinically as referred pain to somatic structures or viscero-visceral hyperalgesia, as recently demonstrated by Brinkert et al. [10] showing intestinal hypersensitivity in dysmenorrhoea patients. The convergence should, however, not be considered as a real physical convergence between the afferents, but rather as a group of neurons which become hyperexcitable in an area of the dorsal horn as a result of the visceral pain signal. This is subsequently perceived as pain in the structures innervated by afferents projecting to the same area in the dorsal horn, for details see [11].

Central pain processing

The afferents travel in the spinothalamic tract to reach the thalamus and cortex. Some travel in the phylogenetically older spinoreticular tract and probably mediate arousal and autonomic responses. Other afferents ascend in the spinomesencephalic tract to reach the midbrain. They are probably related to the periaquaductal grey and influence the descending control systems described below. Recently, fibres travelling in the dorsal column have also been described [2, 12, 13]. The thalamus coordinates and transmits the signals to higher brain centres including primary and secondary somatosensory cortex. From here pain-intensity and pain-localisation are processed. The prefrontal cortex and associated centres are involved in the cognitive processing of pain. Other centres as insula and gyrus cinguli are important for the affective aspects of the pain and are linked to the basal ganglia, the amygdala and the pituitary gland, all of which are involved in the autonomic and neuroendocrine responses [5].

Control systems

The second-order neurons are subject to descending control from higher brain centres. This can be inhibitory as well as excitatory [14]. The balance between the excitatory system and the inhibitory modulation could therefore determine the final interpretation of the pain [9]. Descending inhibition seems to be the major way by which the brain controls pain perception. Several cortical centres are connected to the periaquaductal grey and the raphe magnus nucleus in the medulla being the main player in descending control. Serotonergic neurons project from this nucleus to the spinal cord and form synapsis on inhibitory interneurons. The interneurons inhibit nociception by endogenous opioid release on the projection neurons or the primary afferent in the spinal cord [15, 16].

Sensitisation

Intense or long-lasting pain stimuli or inflammation can lead to plastic changes in the nervous system both in the periphery and at the spinal- and supraspinal level. In the periphery, changes in the chemical environment enhance the nociceptors excitability by increasing response magnitude to stimuli, reducing response threshold and increasing spontaneous activity. Furthermore, normally unresponsive "silent" nociceptors can be activated [17]. All this leads to enhanced visceral input to the spinal cord level which then trigger neuroplastic changes in terms of increased central neuronal activity and excitability (central sensitisation), amplifying the effects of further signals coming from the affected viscus [9] (Fig. 2). The biochemical events are closely linked to phosphorylation of the *N*-methyle-D-aspartate (NMDA) receptor, which results in influx of Ca^{2+} into the cell. This induces local mechanisms such as changes in membrane excitability and generation of nitric oxide and prostanoids, etc. These events lead to an immediate decrease in firing threshold and exacerbate the noxious transmission. In addition, this cascade of events mediates more permanent changes. Thus, immediate early genes such as c-fos are activated, which again form heterodimers that binds to the DNA. This results in production of peptides such as dynorphin and enkephalines in the central nervous system (CNS). These substances seem to initiate more long lasting and complex modulating effects on the central neurons. The alterations in functional structure may therefore result in central plasticity, hyperexcitability and "pain memory", which after some time may be consolidated and independent of the original peripheral input [18].

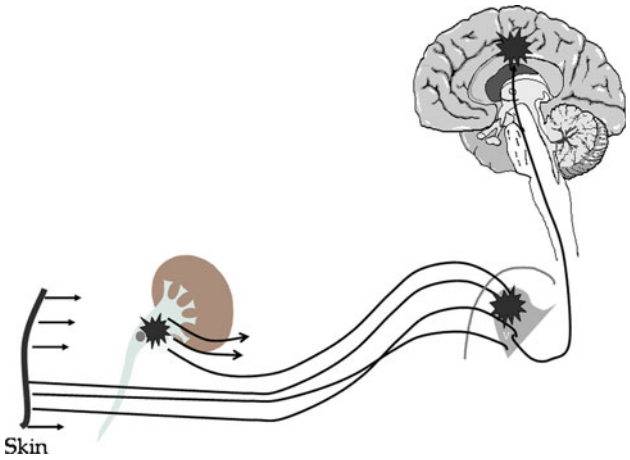

Fig. 2 Afferent visceral fibres may become sensitised by, e.g. endogenous chemicals resulting in an increase in their response magnitude to a given stimulus and/or an increase in the spontaneous activity. The increased afferent barrage activates neurons in the spinal cord and supraspinal centres, resulting in hyperexcitability and increased response to peripheral stimuli

In the brain, there are similar changes as at the lower levels of the nervous system. Furthermore, cortical reorganisation happens, which means that the area that normally processes pain enlarges and involves neighbour areas in the processing of pain [5].

When central sensitisation occurs, the following may be seen in the clinic:

a. allodynia = pain due to a visceral stimulus that does not normally provoke pain.
b. hyperalgesia = increased sensitivity to painful visceral stimuli – decreased pain threshold.
c. Significant increase in the size of the referred pain area together with hyperalgesia of muscle and skin.

Pain processing is without doubt more complex than described here. Certainly, the nervous system is not "hardwired" as described in anatomic textbooks, but undergoes dynamic changes and plastic reorganisation resulting of changes in the clinical picture over time. For more detailed information, the reader is referred to [9].

Pain mechanisms related to the upper urinary tract

Pain from the kidney is usually located to the ipsilateral costovertebral angle just beneath the 12th rib. The pain may radiate across the flank anteriorly towards the upper abdomen and to the groin. Renal pain may be confused with radicular pain as seen with irritation of the costal nerves. The pain distribution is similar, but renal pain is often colicky in nature. Mid-ureter pain is typically referred to the lower left and right quadrant, and to testis/labia. Consequently, the pain may mimic that in appendicitis, diverticulitis or testicular disease. Lower ureteral obstruction usually produces symptoms of bladder irritability (frequency, urgency) and suprapubic pain, which may radiate along the urethra and even the medial thigh [19–21].

Peripheral level

Sensory receptors in the kidney have been classified into mechanoreceptors (activated by increased renal pressure) and chemoreceptors (activated by renal ischemia or changes in the chemical environment/inflammation).

Presumably some chemoreceptors are present in or near the pelvic wall and along the renal vascular system [22]. The presence of a specific nociceptor has not been demonstrated. However, in animal studies, it has been shown that sensory receptors are activated by noxious stimuli such as by occlusion of the renal artery, vein and ureter and by distension of the renal pelvis [22–27]. Mechanoreceptors are located within the renal pelvis and parenchyma and the renal artery, vein and ureter [27]. In the guinea-pig ureter, two populations of mechanosensitive afferents (called U-I and U-II) have been described. U-II was a large group that did not respond to peristalsis but to intense distensions (mean 25 mmHg).They are thought to have nociceptive functions. U-I was a smaller group that responded to contractions in the ureter. They had low thresholds to intraluminal distensions (mean 8 mmHg) and could monitor the peristalsis of ureter [28]. In the renal pelvis and ureteric smooth muscle cells, α- and β-adrenoceptors are represented. While α-adrenergic agent promotes contraction, β-adrenergic agents cause relaxation of the ureter and pelvis [29, 30]. The renal pelvic pressure, normally between 0 and 10 mmHg, depends on tension in the pelvic wall and a rise in pressure can elicit pain as described below [31]. Consequently, α- and β-receptors may have an indirect role in pain mechanisms of the upper urinary tract. Renal afferent nerves composed of Aδ- and C-fibres transmit the signal to the spinal cord [22–26].

In humans, distension of the renal pelvis evokes pain [20], whereas stimulation or pressure applied to the renal capsule or traumatisation of the parenchyma does not cause pain [32, 33]. The afferents only convey pain; there is no recognition of heat and cold [20].

Spinal level

Studies of 2nd order neurons involved in transmission of pain from the upper urinary tract have been performed using either electro-physical or immunohistochemical methods. Nociceptive afferent inputs from different areas of the upper urinary tract are processed in different regions of the spinal cord mainly in dorsal root ganglia L2–L3 and S1–S2 [34]. In rat, electrical stimulation of proximal ureter was recorded in the dorsal horn neurons in L1–L2 and

stimulation of the distal ureter was recorded in the dorsal horn of L6–S1 [35]. In cat, the spinal dorsal horn cell responses to occlusion of the renal artery or ureter were mainly recorded trough T11–L2 [36]. This is in agreement with results in different species, in general [22]. Immunohistochemical methods in rats have documented that stimulation of a kidney by proximal ureteric ligation or increase in the renal interstitial hydrostatic pressure causes activation of both ipsi- and contralateral neurons in the spinal dorsal horn laminae I, II and V [37, 38].

There are reports on pressure threshold in the upper urinary tract eliciting activity in the spinal pain pathway. In a rat-study, cardiovascular responses (taken as a measure of nociceptive response) to distensions of ureter and renal pelvis were found. The responses were proportional to the stimulus' intensity with a threshold of approximately 25 mmHg [39]. In another rat-study, the activation threshold of dorsal horn neurons to distension of the ureter was found to be >20 mmHg. The dorsal horn neurons mainly receive ureteric input from high-threshold afferents (U-II) [40]. These results correlate well with the pain threshold in humans that are reported to be 33 mmHg (range 21–58 mmHg) [41].

Spinal pathway

Ammons et al. have characterised the neuronal response to arterial, venous and ureteric occlusions in cats and monkeys from extensive electrophysiological studies. It was shown that besides the direct connection between renal afferent nerves and the caudal medulla, there exist two additional pathways between the kidney and the brain stem, the spinothalamic and the spinoreticular pathways [23]. Spinoreticular and spinothalamic neurons respond to cutaneous or muscle stimuli (ipsilateral flank and abdomen) in addition to renal stimuli [23, 24, 26, 42]. Renal and ureteric mechanical stimuli which evoke cardiovascular reflexes excite spinoreticular cells [23, 24]. The spinothalamic tract was found to be highly responsive to increases in pressures within the renal pelvis. The pressures are encoding within the noxious range of intensities in humans. This indicates that the spinothalamic tract is involved in pain processing from the kidney [26, 42]. Finally, it was found that spinal neurons with renal input were under the control of tonically active descending pathways [27].

Referred pain area

Giamberardino et al. [43] created a model of artificial ureteric calculus in rats in order to investigate referred pain and hyperalgesia. After surgical exposure, an artificial stone was placed in the upper third of the ureter by injecting dental cement. Rats were then observed for 4–14 days for behaviour indicating visceral pain episodes. The number and duration of pain episodes decreased significantly with time after stone implantation and were mostly visible during the first 3 days. The rats also showed hyperalgesia of the ipsilateral oblique muscle (decreased muscle threshold to electric stimulation), present after the first ureteral crisis, with a maximum on the first 3–4 days after implantation but lasted up to 10 days. There was a correlation between the number of episodes of visceral pain and the extent of muscle hyperalgesia in the sense that hyperalgesia was more accentuated in rats displaying a high number of visceral pain episodes than in those with a smaller number [43]. There was evidence that both the sensory and the sympathetic innervation of the rat-ureter were affected by artificial calculosis. These changes may contribute to the pain-related behaviour [44]. Similar results were found in human studies of patients with ureteric calculi. One study examined eight patients, who had suffered from a few episodes (1–2 attacks) of unilateral stone colic in the upper urinary tract. It was found that the patients had detectable hyperalgesia in the ipsilateral lumbar region in the pain-free interval. Pain thresholds in muscular, subcutaneous and cutaneous tissues to electrical stimulation were significantly lower on the affected side compared to the contralateral side and compared to normal subjects [45]. The data were validated by a stimulus–response relationship as it was shown that in patients who had suffered from a high number of colic episodes, hyperalgesia was much larger than in those who have had a limited number [6]. In a study on nine renal stone patients treated with extra corporeal shock wave lithotripsy (ESWL), it was found that referred hyperalgesia outlasted the elimination of the stone. Before ESWL treatment, the patients had pain thresholds below normal in the skin, subcutaneous tissue and muscle in the lumbar region of the affected side. These thresholds tended to increase progressively with the elimination of stone fragments. Eight months after ESWL, all the patients had eliminated the stone fragments and hyperalgesia had disappeared in the skin, but remained to a mild and moderate extent in the subcutaneous tissue and muscle [46]. Vecchiet et al. also found that hyperalgesia in the muscle produced by upper urinary tract stone disease persisted for months to years after the stone had passed [47].

Referred visceral hypersensitivity has also been studied in infants. Andrews et al. showed that 30 infants with prenatal diagnosed unilateral hydronephrosis had increased abdominal sensitivity compared with 70 control infants. The chance in sensitivity was not dependent on the degree of renal pelvic dilatation. Infants who had corrective surgery (7 patients) continued to display increased abdominal sensitivity after 3 months compared to controls at the same age [48].

Together with hyperalgesia, areas of referred pain from the upper urinary tract are also sites of trophic changes (Fig. 3). In rats, it was shown that referred hyperalgesia was

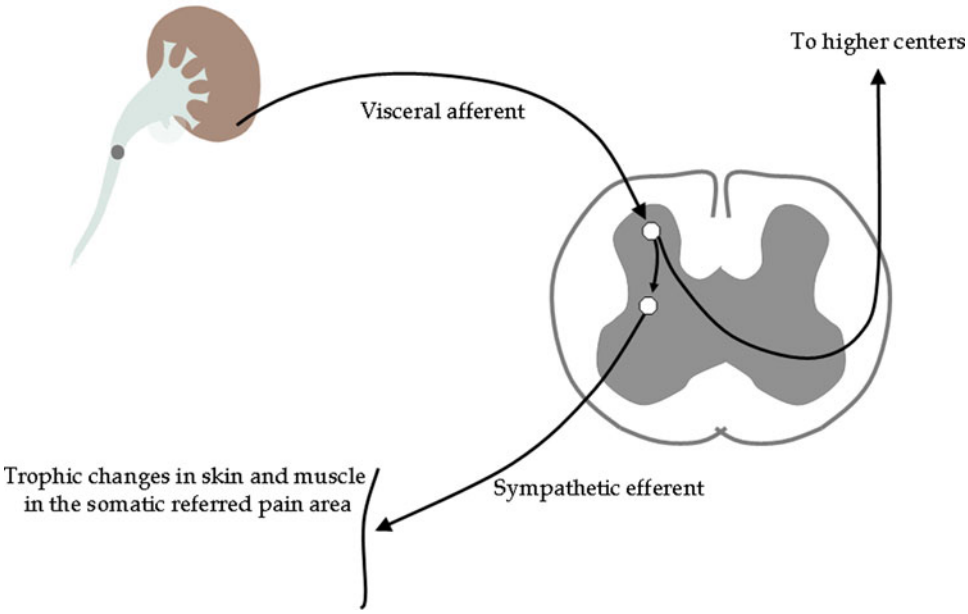

Fig. 3 The autonomic nervous system is involved in blood flow and tone of structures in the skin, subcutis and muscle. Visceral pain may activate reflex archs resulting in long-lasting edema of the skin together with increased muscle tone leading to permanent changes in the somatic structures

accompanied by a state of sustained muscle contraction in the referred area and that the extent of contractions correlated to the number of episodes of stone colic [49]. There is evidence for the muscle contraction being caused by activation of a reflex arc in the spinal cord [50]. In humans with unilateral urinary stones, it was shown that thickness of the subcutis on the affected side in symptomatic patients was significantly greater than in the contralateral side, and the muscle thickness was significantly lower when measured with ultrasound [6]. Sustained muscle contraction as a consequence of urinary tract stimulation has also been described in humans. In 29 persons, it was found that electrical, mechanical or thermal stimulation of the ureter and kidney pelvis (trough a cystoscope and ureteric catheters) were accompanied by referred pain and painful contractions of abdominal and loin muscles, which outlasted the stimulus [20].

The contribution to the pain from changes in ureteric motility caused by an artificial calculus has also been examined. In rat studies, ureteric motility as well as changes in intraureteric pressure was measured 1, 4 and 8 days after an artificial stone implantation. Partial ureteric obstruction produced hypermotility and the pressures reached during contractions were equivalent to those evoking nociceptive reactions in animals and humans. The hypermotility persisted even after the stone was eliminated [51].

In summary, patients with upper urinary tract stones develop hypersensitivity in the lumbar region. This hypersensitivity appears soon after the first painful episodes and is accentuated by repeated episodes of stone colic. It is present in pain-free periods and outlasts stone elimination. Trophic changes and muscle contractions are also present in the referred pain area. These findings explain why recurrent stone patients may experience the stone colic to be more and more severe, and explain why even small stones in a patient with recurrent stone may cause severe pain.

Viscero-visceral hyperalgesia

Giamberardino et al. have investigated viscero-visceral hyperalgesia caused by ureter pain in rats and humans. In their first study, they examined estrous differences in the characteristics of stone colic in animals with an artificial ureteric stone. An enhancement of ureteral pain sensitivity in metestrus/diestrus (perimenstrual period) was found. They concluded that this could be related to both hormonal changes and the connection between nerves supplying reproductive organs and urinary tract (afferents from uterus and upper urinary tract enter the same spinal cord segments) [52]. In a further study, two groups of rats were compared. In both groups, an artificial stone was implanted in one ureter. Furthermore, one of the groups had an endometriotic cyst implanted (mimicking endometriosis), whereas the other group had sham endometriosis. In the group with endometriosis increased pain crisis and muscle hyperalgesia was found [53]. These studies are in agreement with a human study in which 69 fertile women afflicted by stone formation of the upper urinary tract were investigated. Dysmenorrheic women reported more episodes of colic than non-dysmenorrheic women, and women with previous dysmenorrhea treated with estroprogestins. Pain thresholds (electrical stimulation) of the oblique musculature ipsilateral to the stone were lower in the dysmenorrheic women compared to the non-dysmenorrheic and the previous dysmenorrheic women. This shows that painful conditions of the female reproductive

organs enhance pain and referred hyperalgesia from the upper urinary tract. The authors hypothesised that the explanation for this phenomenon is an increased afferent barrage from the reproductive organs towards the central nervous system. This increases the excitability of viscero-visceral convergent neurons in the spinal cord, so that the central effect of the input from the upper urinary tract is amplified [54].

Sensitisation

In rats with an artificial stone in the upper ureter, changes in cell activity were studied in the spinal cord (T11–T12) and data were compared with those recorded in control rats. The stones resulted in muscular hyperalgesia. Stone-rats with high degree of muscle hyperalgesia presented significant cell hyperactivity in the dorsal/intermediate spinal cord indicating that muscle hyperalgesia is accompanied by a state of central sensitization probably triggered by abnormal afferent input from the visceral focus [55]. This is in agreement with a rat study by Roza et al., who described excitability changes (enhanced background activity, greater number of ureter-driven cells, and decreased threshold of convergent somatic receptive fields) of spinal neurons receiving ureteric input when exposed to an artificial stone in the ureter. They concluded that this probably accounted for the referred muscle hyperalgesia seen in the same rats [56]. NMDA receptor antagonists were found to inhibit nociceptive reflexes evoked by graded distensions of the cannulated ureter in rats. This leads to the conclusion that acute stimulation of normal ureter provokes intense responses that recruit neural mechanisms mediated by NMDA receptors as described in the previous section about sensitisation in general [57].

Supra-spinal level

Only a few data exist on the supraspinal pain processing from the upper urinary tract.

Ammons et al. have described activity in the brain stem in cats in response to arterial, venous and ureteric occlusions. They showed that the ventrolateral medulla is affected by activation of renal mechano- and chemoreceptors [25]. Other animal studies have found that renal information also alters the activity in neurons in the reticular formation, nucleus of solitary tract, hypothalamus [23] and thalamus [58].

Together with the periaqueductal grey, the nucleus raphe magnus (NRM) is known to be a potent pain inhibitory centre. In a study on cats, the role of NRM in renal pain was examined. The study showed that stimulation of NRM inhibited the activities of spinal dorsal horn neurons evoked by renal pain (occlusion of the ureter or renal artery). The same spinal dorsal horn neurons were all found to have somatic peripheral receptive fields. Stimulation of NRM also inhibited the activities of the spinal dorsal horn neurons evoked by noxious stimulation of these fields [59]. Knuepfer et al. [60] have also found that stimulation of NRM lead to reduced activity of spinal dorsal horn neurons evoked by afferent renal nerve stimulation (Fig. 4). Descending control likely also plays a role in the different manifestations of urological diseases in humans, although it still needs to be demonstrated in experimental studies.

Pharmacological modulation

To study pharmacological treatment of pain and hyperalgesia in urinary colic caused by stones, Giamberardino et al. used the rat-model previously mentioned. They found that tramadol and morphine administrated in a prolonged fashion (4 days) significantly reduced the number and duration of the stone crises dose-dependently [43, 61, 62]. Similarly, prolonged administration of ketoprofen [a non-steroid anti-inflammatory drug (NSAID)], hyoscine-*N*-butylbromide (a spasmolytic anticholinergic) or both drugs in combination significantly reduced the referred hyperalgesia [61, 63]. Metamizol (a NSAID) treatment also dose-dependently decreased the duration and the number of crises in the same model. In addition, it inhibited the abnormal ureteric peristalsis and the activity of the nociceptive dorsal horn neurons [64]. Similar results were obtained in studies in dogs and sheep in which NSAIDs decrease ureteral peristaltic

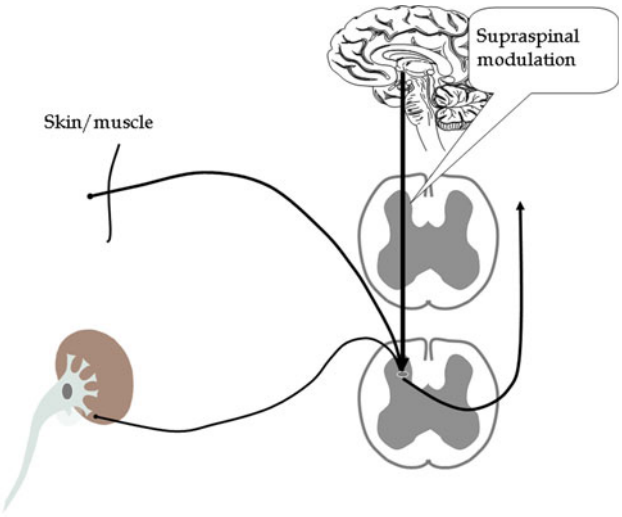

Fig. 4 The incoming pain signal can be modulated by different nociceptive control mechanisms. Descending inhibitory (and exhibitory) pathways from the brain and interaction between somatic and visceral nerves on the spinal level are present

frequency in an obstructed kidney. Furthermore, it was found that the pressure in the obstructed renal pelvis was decreased [65–68]. These factors may contribute to the pain relief produced by NSAIDs.

Decreasing the renal pelvic pressure by modulating muscle activity could be another target in pain management. α- blockers and Ca-antagonists have appeared potent in relaxing human ureteric smooth muscles [69]. Furthermore, they enhanced the clearance of lower ureteral stones and reduced the need for analgesic therapy [70, 71].

Upper urinary tract distension causes visceral pain and a reduction of mean arterial blood pressure in rats. This pressure response was used to study the analgesic effect of morphine. It was found that morphine abolished the pressure response dose-dependently. Naloxone inhibited the effect of morphine [39, 72]. In humans, NSAIDs and opioids are the commonly used drugs in the treatment of renal colic [73]. A review compared the efficacy of NSAID (indomethacin, diclofenac, keterolac, tenoxiam, indoprofen) versus opioids (pethidine, morphine, meperidine, oxycodone, pentazocine, ketogan, tramadol, hydromorphine) in the treatment of acute renal colic. Both types of drugs led to clinically important pain reductions. Patients receiving NSAIDs achieved greater reductions in pain scores and were less likely to need rescue analgesia in the short term than those receiving opioids. Furthermore, opioids were associated with a higher incidence of adverse effects, especially vomiting [74]. Consequently, NSAID was regarded as the drug of choice for treatment of renal colic. Recently, however, several studies have showed a relationship between NSAID treatment and the risk of death and myocardial infarction besides the well-known adverse effects on the gastrointestinal tract. Caution, therefore, should be exercised in chronic NSAID use [75–78]. Furthermore, in case of severe pain, NSAID may not be sufficient and an opioid may be needed. To our knowledge, there is no evidence as to which opioid is most effective with fewest side effects. In a study in healthy volunteers, oxycodone was superior to morphine in alleviating visceral pain [79]. Different pharmacological profiles of the drugs were thought to be the explanation as animal studies suggested that oxycodone mediates its effect not only by μ-receptors (as does morphine) but probably also by κ-receptors only localised on visceral afferents [80, 81]. The analgetic effect of oxycodone was more correlated to plasma concentrations compared to morphine that works in the central nervous system compartment. This indicates that oxycodone has an effect in the periphery perhaps mediated via κ-receptors [82]. In a study of patients following abdominal surgery, pain relief was achieved with less oxycodone than morphine and the effect occurred faster and lasted longer [83]. Since pain from the upper urinary tract may be regarded as "true" visceral pain there may be a differential effect of the opioids on these diseases as well, but this is still speculative and awaits confirmation in future studies.

Non-pharmacological modulation

A few investigations have been published on non-pharmacological treatment of visceral pain in the upper urinary tract. In a study of humans, it was found that local active warming (abdomen and lower back region) during emergency transport is an effective treatment of pain caused by kidney stones. Furthermore, decreased nausea and anxiety was observed. The authors hypothesised that these results probably are due to convergence between heat afferents from the body wall and visceral afferent that may alter central viscero-sensory processing in the dorsal column resulting in anti-nociceptive input [84].

The effect of transcutaneous electrical nerve stimulation (TENS) has been studied in renal pain in cats. The mechanisms of pain relief by TENS are believed to be associated with activation of inhibitory pain mechanisms as described above [85]. The renal pain was induced by acute occlusion of the ureter or renal artery. It was found that TENS reduced the activity of dorsal horn cells induced by ureteric occlusion or renal arterial occlusion for a period of 10 min. TENS also reduced the activity of dorsal horn cells induced by somatic stimulation of the receptive fields of the skin [36]. Comparable results have been reported for humans in whom local TENS was found to alleviate renal colic pain and anxiety in a randomised double-blinded study with 73 patients. Furthermore, it was found that nausea and heart rate was decreased as an indirect sign of decreased sympathetic nerve activity [86].

Pain inhibitory systems including diffuse noxious inhibitory control are also possible explanations for the analgetic effect of intracutaneous injection of sterile water and acupuncture in the treatment of renal colic in patients. The studies concerning intracutaneous injection of sterile water were obtained in double-blinded randomised trails with a total of 132 patients. It was found that the treatment effectively inhibited renal colic pain [87, 88]. In the acupuncture studies, acupuncture was compared with intramuscular injection of avafortan, morphine and bucinnazine [89, 90]. The results showed that acupuncture was better than or as effective as the analgesic in relieving renal colic, but the studies were not blinded and results should be interpreted carefully.

Conclusion

Pain originating from the upper urinary tract is among the most intense forms of pain in man and has all the characteristics of visceral pain. The pain pathways, sensitisation,

referred pain with or without hyperalgesia/trophic changes and viscero-visceral hyperalgesia have been relatively well explored, but visceral pain mechanisms in humans has not yet been sufficiently unravelled. Since upper urinary tract pain seems to be representative of true visceral pain, further studies in this area may not just give valuable information on how to treat upper urinary tract pain better, but also contribute to the understanding of visceral pain mechanism in general.

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