Review Article

Urine Trouble: Alterations in Brain Function Associated with Bladder Pain

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Abbreviations and Acronyms

BPS = bladder pain syndrome

CeA = central nucleus of the amygdala

CNS = central nervous system

CORT = corticosterone

CP/CPPS = chronic prostatitis/chronic pelvic pain syndrome

CRH = corticotropin releasing hormone

CYP = cyclophosphamide

IC = interstitial cystitis

PAG = periaqueductal gray

PBn = parabrachial nucleus

PMC = pontine micturition center

PVN = paraventricular nucleus of the hypothalamus

RVM = rostral ventromedial medulla

SI = primary somatosensory cortex

SPT = spinoparabrachial tract

STT = spinothalamic tract

UBD = urinary bladder distension

VPL = ventroposterolateral nucleus of thalamus

Purpose: Chronic bladder pain is a debilitating condition often accompanied by alterations in affective and autonomic function. Many symptoms associated with chronic bladder pain are mediated by the central nervous system. In this review data from preclinical animal models and human neuroimaging studies were analyzed and a theoretical supraspinal bladder pain network was generated.

Materials and Methods: We comprehensively reviewed the literature using PubMed® and Google Scholar™. Relevant reviews and original research articles, and the cited references were summarized and then organized on a neuroanatomical basis.

Results: The brain loci the most predominant in the bladder pain literature are the thalamus, parabrachial nucleus, cerebral cortex, amygdala, hypothalamus, periaqueductal gray and rostral ventromedial medulla. This review highlights each of these regions, discussing the molecular and physiological changes that occur in each in the context of bladder pain.

Conclusions: A complex network of brain loci is involved in bladder pain modulation. Studying these brain regions and the changes that they undergo during the transition from acute to chronic bladder pain will provide novel therapeutic strategies for patients with chronic bladder pain diseases such as interstitial cystitis/bladder pain syndrome and chronic prostatitis/chronic pelvic pain syndrome.

Key Words: urinary bladder, brain, pain, neuroimaging, central nervous system

THE brain is responsible for integrating the sensory and the affective components of bladder pain. Many of the hallmarks associated with chronic bladder pain are mediated by the CNS. For instance, bladder pain is diffuse and referred to somatic structures such as the knees and lower back due to the convergence of multiple primary sensory afferents on second order neurons within the spinal cord.[1] Bladder pain is also

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associated with strong autonomic and emotional responses, implying the involvement of higher order processing in the brain itself. Undoubtedly, the peripheral nervous system has a large role in acute bladder pain processing. Intravesical lidocaine regimens ameliorate bladder pain for up to 10 days following application.[2]

However, during the transition from acute to chronic bladder pain a network of nociceptive brain centers is recruited to sustain pain despite a lack of constant peripheral input. Furthermore, it is likely that in the absence of effective alleviation of symptoms the brain is responsible for frequent comorbidities associated with chronic bladder pain, including depression, anxiety and cognitive changes.[3]

Although numerous studies have evaluated the role of the brain in processing and mediating aspects of somatic pain, exploration of the CNS in IC/BPS and other visceral conditions is relatively limited. A number of important distinctions between somatic and visceral pain suggest that extrapolating data from somatic studies to visceral pain may not be appropriate. These distinctions include the relatively low innervation of the viscera by primary sensory afferents, the lack of conscious perception of visceral nociceptor activation, the broad arborization of visceral afferents in the spinal cord, the independent nerve networks in visceral organs and the distinct spinal projection tracts among others.[1]

Chronic bladder pain is most commonly diagnosed as IC/BPS or CP/CPPS. The specific cause of these diseases is unknown and patients are only diagnosed with the disease after all other pelvic conditions with known pathologies are excluded. Research efforts have focused on addressing bladder pain from within the organ itself. However, new evidence suggests that the brain has a critical role in bladder pain maintenance and should be further investigated as a therapeutic target. This review summarizes what is currently known about the involvement of the brain and the brain stem in bladder pain processing.

MATERIALS AND METHODS

A comprehensive literature review was performed using PubMed and Google Scholar. Key words included supraspinal, central nervous system, brain, brainstem, bladder pain and bladder nociception. Secondary searches were completed using the keywords thalamus, parabrachial nucleus, cortex, hypothalamus, amygdala, periaqueductal gray, rostral ventral medulla and bladder pain after these brain regions had been identified in the primary literature search. Articles written in a language other than English were not included in analysis. Relevant reviews and original research articles, and the cited references were summarized and then organized on a neuroanatomical basis.

RESULTS

The complex neuroanatomical profile of bladder pain starts at the level of the primary afferent and compounds as it ascends to the brain. Sensory information from the bladder is detected by lightly myelinated Aδ and unmyelinated C fibers carried in the hypogastric, pelvic and pudendal nerves.[4] Second order neurons receiving visceral input are primarily located in the superficial dorsal horn (laminae I and II), and laminae V and X of the spinal cord.[1] The 3 main ascending tracts that visceral information is conveyed through are the STT, the SPT and the dorsal column pathway (see figure).

The remainder of this review highlights the major supraspinal sites that have been linked to bladder pain in preclinical animal models and imaging studies in patients with chronic bladder pain.

Thalamus

As the termination point of the STT the thalamus is one of the first supraspinal sites involved in bladder pain processing. Recent imaging studies have revealed that women with chronic pelvic pain show decreases in left thalamus gray matter compared to healthy controls.[5] Additionally, diffusion tensor imaging revealed decreased fractional anisotropy (ie reduced white matter integrity) in the right anterior thalamic radiation to the prefrontal cortex, which correlated with increased pain and urinary dysfunction, and decreased quality of life in patients with IC/BPS.[6]

In macaques UBD primarily increases activity in VPL neurons, of which some directly projects to the primary somatosensory cortex.[7] Conversely, a second smaller population of VPL cells is inhibited during UBD. However, both populations show analogous changes in activity during noxious somatic stimulation of the lower body (ie tail, groin and hip regions) and innocuous somatic stimuli does not alter cell excitability.[7] In the cat and rat UBD also excites and inhibits distinct populations of cells in the ventrobasal thalamic nucleus, a more broad anatomical area that encompasses the VPL.[8,9] However, unlike in the monkey, these cells also respond to innocuous and noxious somatic stimuli, suggesting that there are species specific differences in thalamic mediation of peripheral inputs. Furthering this species specificity is the fact that UBD evoked changes in neuronal activity were blocked by lesioning the dorsal midline of the rat spinal cord, suggesting that nociceptive information from the bladder in this species is primarily transmitted to the ventrobasal group of the thalamus via the dorsal column pathway and not via the traditional STT.[9]

Cellular activation as measured by transcriptional increases in the immediate early gene cFos was noted in the paraventricular and mediodorsal nuclei of the mouse thalamus 1 and 2 hours after injection with CYP, a cystitis inducing compound.[10] Increased