To assess ongoing pain, the pain intensity was measured by visual analogue (VAS) scale. During and immediately after the CPT, the subjective pain threshold, pain tolerance, and mean NFR area were determined again.

The aim of the study was to clarify N/OFQ selectivity for noxious evoked activity and site of action, which is advisable for its possible therapeutic use as a potential drug in treatment of sensory disorders of micturition and painful bladder syndromes.

**Study design, materials and methods**

To assess the influence of acute intravesical instillation of N/OFQ on the spinal nociceptive reflex and to evaluate the supraspinal modulation of nociceptive pathway to the bladder we performed neurophysiological evaluation of a purely nociceptive reflex, the nociceptive flexion (RIII) reflex (NFR), in 3 healthy subject and 4 patients with hypersensitivity bladder dysfunction (1 pt with neurogenic incontinence due to incomplete spinal cord lesion, 1 pt idiopathic detrusor overactivity, 1 pt idiopathic urinary retention).

The NFR was recorded from the biceps femoris muscle in response to stimulation of the sural nerve with a train of 5 unipolar rectangular 1 ms pulses, with 200 Hz of rate, with intensity 1.2 times the subjective pain threshold. The NFR reflex threshold and the mean area with suprathreshold stimulation were determined.

To assess ongoing pain, the pain intensity was measured by visual analogue (VAS) scale. During and immediately after the CPT, the subjective pain threshold, pain tolerance, and mean NFR area were determined again.

The same procedure was repeated 30 minutes after intravesical instillation of 1 microM of N/OFQ.

**Results**

A significant increase in NFR threshold and a reduction of subjective pain perception threshold was observed after instillation of N/OFQ and CPT in all pts except one with cervical incomplete SCI, in whom N/OFQ instillation caused a reduction in NFR threshold associated with a disesthesia at upper limbs.

In controls a reduction in NFR and subjective pain threshold was present only during CPT.

**Interpretation of results**

NFR is the most used nociceptive reflex and appears to be most reliable in assessing treatment efficacy because it is exclusively mediated by nociceptive afferents and is suppressed by the antinociceptive systems and analgesic drugs. Although the NFR has been used to assess efficacy of opiates, NSAIDs, hypnosis, and neurostimulation procedures, there aren’t experience neither in patients suffering from hypersensitive bladder dysfunction nor in N/OFQ use for LUT dysfunction.

The NFR is a polysynaptic reflex that allows withdrawal from noxious stimuli. It can be elicited by electrical stimulation of a sensory nerve (sural nerve) at a strength sufficient to depolarize nociceptive afferents (Aδ fibers): after the nociceptive input an extensive processing takes place within the spinal cord, involving the primary sensory neurons to the motor neurons in a polysynaptic pathway.

Therefore, other afferent input, descending activity, and the excitability of the neurons in this pathway modulate the generation of the spinal nociceptive reflex.

NFR displays a two part response in the ipsilateral biceps femoris muscle: the short latency part of the response (RII) is a result of stimulation of low threshold cutaneous fibers, while the longer latency component (RIII) is evoked by higher stimulation intensities that activate Aδ and C fibers responsible for the transmission of nociceptive impulses.

Studies in healthy volunteers suggested that the classical counter-irritation phenomenon (i.e. pain inhibits pain effect) might depend on diffuse noxious inhibitory controls (DNIC), which modulate the spinal transmission of nociceptive signals.

DNIC represents a segmental spinal cord as well as supraspinal modulatory mechanism of nociception whose effect last until conditioning stimulus is present. In normal subjects, heterotopic painful stimuli induce simultaneous and
parallel decreases in the subjective sensation of pain and in the NFR evoked by electrical stimulation of the sural nerve.

While supraspinal influence on DNIC involve the caudal medulla, including the subnucleus reticularis dorsalis, the inhibition of NFR is not evoked in cervical complete spinal cord injury patients.

Concluding message

In these preliminary observations it seems that both N/OFQ and DNICs were able to modify the perception of pain suggesting that DNICs and N/OFQ use the same descending inhibitory pathways for the control of pain. Our data indicate that under normal conditions the N/OFQ modulation of the nociceptive reflex is not functionally active whereas in neurogenic LUT the N/OFQ exert a tonic inhibitory modulation of the nociceptive reflex that is mediated by descending pathways. The presence and the level of SCI seem to be a critical factor in N/OFQ modulation of nociceptive pathway.

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