225

Malaguti S[1], Lazzeri M[2], Spinelli M[1], Zanollo L[1]
1. spinal unit niguarda hospital, 2. urology santa chiara hospital florence

NEUROPHYSIOLOGICAL NOCICEPTIVE FLEXION (RIII) REFLEX EVALUATION DURING INTRAVESCICALLY ADMINISTRATION OF N/OFQ: HYPOTHESIS ON MECHANISM AND SITE OF ACTION IN HUMANS.

Hypothesis / aims of study

In patients with neurogenic incontinence the robust acute inhibitory effect on the micturition reflex caused by the activation of orphan opioid receptor-like (NOP), applies the peptide nociceptin (N/OFQ) as potential novel drugs for the treatment of neurogenic urinary incontinence.

N/OFQ inhibits the micturition reflex at a peripheral and supraspinal site: to act at peripheral level the functional integrity of capsaicin-sensitive bladder afferents is required when intravenously administred, while a direct effect on ORL1 receptors located in the pontine micturition center is postulated for the supraspinal effect on both the afferent and the efferent pathways of the micturition reflex.

The physiological role of N/OFQ in the effect of nociception on spinal reflexes and in the modulation of pain perception is still an argument because of both facilitatory pronociceptive (hyperalgesia) and inhibitory-antinociceptive actions observed in pharmacological experiments.

In positron emission tomography imaging studies in humans confirmed the key role of the periaqueductal grey matter as important sensory relay center for bladder afferent.

However in human experimental pain research only neurophysiological assessment of nociceptive reflex allows to apply quantitative and standardized somatic stimulations capable to activate nociceptors and then record and quantify the evoked response.

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 intravescical 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 hypersensity bladder dysfunction (1 pt with neurogenic incontinence due to incomplete spinal cord lesion, 1 pt idiopathic detrusor overactivity, 1 pt idiopathic urinary retention).

To investigate counter-irritation mechanisms we analysed the NFR and the concomitant cold pressor test (CPT) used as an heterotopic nociceptive stimulation.

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 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 intravescical 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 (A δ 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.

FUNDING: NONE
DISCLOSURES: NONE
HUMAN SUBJECTS: This study was approved by the niguarda hospital and followed the Declaration of Helsinki Informed consent was obtained from the patients.