Neurophysiological approach to central pain modulation in primary headaches

Abstract The study of CNS pain-modulating pathways has led to important discoveries about the role of central nociceptive structures such as PAG and hypothalamus in the pathophysiology of episodic and chronic primary headaches. Functional neuroimaging studies have revealed that primary headaches are characterised by different patterns of activation of central pain modulatory structures. A future model of headache pathophysiology investigating the contribution of CNS pain-modulating pathways will probably increase our understanding of pain processing in primary headaches. Herein we review the neurophysiological approaches to assess central pain modulation in primary headaches with emphasis on the diffuse noxious inhibitory control, a form of endogenous pain inhibition. In addition, patients’ data will be presented that highlights the utility of such methods for primary headache’s pathophysiology and clinical monitoring.

Key words Headache • Neurophysiology • DNIC • Central pain modulation

Introduction

Progress in pain research has definitively established that pain is not automatically transmitted from the periphery to the brain. The pain signalling system consists of several channels with many synaptic relays, feedback circuits and a high degree of plasticity. From the first synapse the pain signal is under a powerful modulatory control adapting pain perception to the external and internal environmental needs.

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Descending control of pain. Diffuse noxious inhibitory control

Pain descending modulatory pathways represent a complex network of supraspinal structures operating with both direct and indirect facilitatory and inhibitory pathways on spinal cord and trigeminal primary nociceptive afferents [3]. The physiological role of these systems is to potentiate or suppress nociceptive messages to the brain as a function of internal and external environments of the organism. Supraspinal pain modulation may be dynamically investigated by examining the diffuse noxious inhibitory control (DNIC) [4]. DNIC may be defined as the inhibition of nociceptive neurons in the spinal and trigeminal dorsal horns produced by a noxious stimulus applied in any part of the body distant from the neuron’s excitatory receptive field [4]. Anatomical and electrophysiological studies indicate that DNIC results from a complex spino-bulbo-spinal loop, specifically activated by A-delta and C peripheral fibres [4]. The brainstem, namely the medullary reticular formation, is the key neuronal link of the loop subserving DNICs. It has been shown that the RIII reflex as well as the perception of pain are strongly inhibited by DNIC systems [5]. There is a common opinion that the wide dynamic neurons are the principal site where the DNICs exert their inhibitory modulation. As such neurons are activated in unpredictable but permanent ways by all non-noxious and noxious stimuli, it has been postulated that the resulting “basic somaesthetic activity” when transmitted to higher centres could constitute a “noise”, from which these centres would have difficulty extracting a clear signal of pain. In this view, DNICs could provide the filter which would allow such an extraction to be achieved [4, 5].

Very recently Edwards et al. [6] have demonstrated that DNIC measurements are a consistent predictor of clinical pain and physical health highlighting the potential clinical relevance of DNIC in the field of pain clinical neurophysiology. Accordingly, a dysfunction of DNIC mechanisms has been found in patients with different forms of chronic painful disorders [7, 8]. It has been supposed that a defective DNIC activity may induce a consequent facilitation of central sensitisation leading to chronic pain syndromes [7]. A recent study of our research group [9], which investigated in detail the inhibitory effect exerted by DNICs on the temporal summation of the RIII in humans, revealed a gender-specific inhibition of the temporal summation threshold of the RIII reflex in healthy subjects. These findings strongly support the notion that the supraspinal modulation of pain sensation and pain-related reflex effects prompted by DNICs are not limited to the inhibition of pain transmission, but may also be involved in regulating the development of the neuronal plasticity of nociceptive neurons. In the last few years we have performed several research studies with the aim of defining the pathogenetic role of pain-modulating systems subserving DNIC in primary headaches and their usefulness in clinical neurophysiology of the headache.

DNICs in migraine and chronic tension-type headache patients

DNIC was examined in 24 migraineurs without aura, 17 patients with chronic tension-type headache (CTTH) and 20 healthy subjects by means of nociceptive flexion RIII reflex and the cold pressor test (CPT) as heterotopic noxious conditioning stimulation (HNCS) [10]. The subjective pain thresholds (Tp) and the RIII reflex threshold (Tr) were significantly lower in CTTH vs. controls. In controls a significant inhibition of the RIII reflex was observed during CPT (~30%, p<0.05). Conversely, migraine and CTTH patients showed facilitation (+31%, p<0.05 and +40%, p<0.01, respectively) of the RIII reflex during the HNCS. The present study demonstrates a dysfunction in systems subserving DNIC in headache patients. Our findings may be interpreted as the result of the prevalence of descending facilitatory influences activated in the setting of an acute noxious stimulation, such as CPT. We suggest that an impairment of endogenous supraspinal pain modulation systems may be an important common denominator in the pain mechanism of both CTTH and migraine. In the former, the increased facilitation and decreased inhibition of pain transmission at a brainstem level may be secondary to prolonged nociceptive inputs from peripheral myofascial tissues; in the latter, the same pattern of supraspinal pain modulation may be the result of a primary dysfunction of brainstem nuclei. Impairment of endogenous supraspinal pain modulation systems may
contribute to the development and/or maintenance of central sensitisation in primary headaches.

**Descending inhibitory control on nociceptive trigeminal-mediated responses in migraine with and without aura**

We investigated the DNICs’ function in the interictal period of 43 patients suffering from migraine without aura and with aura (n=11) [11] by studying the trigemino-cervical (TCR) and the trigemino-spinal responses (TSR). Such reflexes have shown to be markedly inhibited by activation of the DNIC system by means of CPT [12]. The recovery curve of TCRs was significantly faster in migraine patients than in controls. The recovery curve of TSR was normal. Activation of the DNICs through the CPT significantly reduced the TCRs and TSRs area in both migraine patients and controls and the extent of this reduction did not differ significantly between migraineurs and controls (all \( p > 0.05 \)). No correlation was found between TCR/TSR neurophysiological parameters and DNIC activity. These data suggest that migraine patients, in the interictal phase, are characterised by a specific, abnormal, interictal hyperexcitability of the neuronal substrate that mediates TCR whereas endogenous supraspinal pain modulation is activated similarly to normal subjects. These findings are contrasting with those reported before. These discrepancies may be explained by the use of different population of migraineurs and that the pain-induced motor responses recruitment in cranio-facial region is more variable than in other districts. From a theoretical point of view, DNIC activity could be related to specific migraine phenotypes such as the presence/absence of allodynic attacks, a hypothesis we are currently investigating.

**Effect of DNICs on temporal summation of the nociceptive flexion reflex in medication-overuse headache**

The RIII reflex threshold (Th), and the RIII temporal summation threshold (TST) were investigated at baseline and during activation of DNIC in 23 patients diagnosed as having migraine+medication-overuse headache (MOH), and 20 healthy controls. MOH patients were examined before and after a standardised detoxification programme.

Before detoxification, a significantly lower RIII Th and TST were found in MOH vs. controls (mean values 9.78 vs. 15.4 and 8.6 vs. 13.2, \( p < 0.01 \)); in these patients CPT induced a significantly (\( p < 0.01 \)) lower TST increase and RIII inhibition compared with controls. The psychophysical results paralleled neurophysiological findings. After detoxification RIII TST and CPT effect on TST were normalised whereas RIII Th and CPT effect on RIII improved but remained significantly different from control values. These data suggest that MO-induced chronification of migraine determines a central sensitisation and an enhanced temporal integration of nociceptive stimuli alone with a hypofunction of DNIC. Such abnormalities are partially and differently reverted after detoxification.

**Conclusions**

DNIC is a valuable neurophysiological method for investigating central pain modulation in primary headaches. Additional research is necessary to further our understanding of the pathophysiological role of DNIC in primary headaches and its contribution to the development or maintenance of central sensitisation.

**References**

1. Nappi G, Rossi P (2004) Pathophysiology of migraine. In: Nappi G, Rossi P (eds) Migraine: current concepts. Current Medical Literature, London, pp 54–64
2. May A (2003) Headache: lessons learned from functional imaging. Br Med Bull 65:223–234
3. Millan MJ (2002) Descending control of pain. Prog Neurobiol 66:355–474
4. Willer JC, Bouhassira D, Le Bars D (1999) Bases neurophysiologiques du phénomène de contre-irritation: les controles inhibiteurs diffus induits par stimulations nociceptives. Neurophysiol Clin 29:379–400
5. Willer JC, De Broucker T, Le Bars D (1989) Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. J Neurophysiol 62:1028–1038
6. Edwards RR, Ness TJ, Weigent DA, Fillingim RB (2003) Individual differences in diffuse noxious inhibitory controls (DNIC): association with clinical variables. Pain 106:427–437
7. Kosek E, Ordeberg G (2000) Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following surgical pain relief. Pain 88:69–78
8. Desmeules JA, Cedraschi C, Rapiti E et al (2003) Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum 48:1420–1429
9. Serrao M, Rossi P, Sandrini G et al (2004) Effects of diffuse noxious inhibitory controls on temporal summation of the RIII reflex in humans. Pain 112:353–360
10. Rossi P, Sandrini G et al (2003) Abnormal modulatory influence (facilitation instead of inhibition) by diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. Cephalalgia 23:741
11. Serrao M, Perrotta A, Bartolo M et al (2005) Enhanced recovery cycle of trigemino-cervical-spinal reflexes in migraine patients during the pain-free period. Headache (in press)
12. Serrao M, Rossi P, Parisi L et al (2003) Trigemino-cervical-spinal reflexes in humans. Clin Neurophysiol 114:1697–1703