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Abnormal spinal cord pain processing in Huntington's disease. The role of the diffuse noxious inhibitory control

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HIGHLIGHTS

- Huntington's disease patients showed abnormalities in the temporal processing of the nociceptive stimuli at spinal level.
- In Huntington's disease patients the supraspinal control of pain expressed by diffuse noxious inhibitory control seems to work normally.
- Our data support the hypothesis that the striatum is involved in pain matrix and that its atrophy could interfere with pain processing.

ABSTRACT

Objectives: Our study is aimed to evaluate the spinal cord pain processing in Huntington's disease (HD) by testing both the temporal summation threshold (TST) of the nociceptive withdrawal reflex (NWR) and the functional activity of the diffuse noxious inhibitory control (DNIC) as form of supraspinal control of pain.
Methods: We enrolled 19 HD patients and 17 healthy controls. We measured threshold (Th), Area, TST and related psychophysical pain sensations of the NWR, at baseline and during and after activation of the DNIC by means of cold pressor test (CPT) as heterotopic noxious conditioning stimulation.
Results: In HD patients we found a significantly higher Th and TST as well as a lower Area when compared to controls. During the CPT, a significant inhibition of reflex and psychophysical pain responses were found in both HD patients and controls when compared to baseline, without differences between the groups in CPT results.
Conclusions: Our study demonstrated an abnormal spinal cord pain processing in HD patients. Abnormalities in pain processing are not apparently linked to a dysfunctional DNIC inhibitory projection system in HD patients.
Significance: Our findings support the hypothesis that the striatum could play a role in pain modulation and that its atrophy could affect pain processing without change the DNIC efficiency.

1. Introduction

Huntington's disease (HD) is an autosomal dominant, fully penetrant, neurodegenerative disorder, characterized by a progressive neuronal loss in the striatum that results in a characteristic triad of symptoms, commonly including movement disorders (usually chorea), cognitive involvement (dementia) and psychiatric symptoms (Ross and Tabrizi, 2011). In our clinical experience, HD patients very rarely complaint for spontaneous pain, although very poor attention has been addressed to pain symptoms in this degenerative disorder (Albin and Young, 1988). In other basal ganglia degenerative pathologies, including Parkinson's disease (PD), an high prevalence of pain symptoms (Chudler and Dong, 1995; Defazio et al., 2008), as well as abnormalities in pain processing (Perrotta et al., 2005 and Perrotta et al., 2011a; Bartolo et al., 2008; Tinazzi et al., 2008; Serrao et al., 2011), have been clearly demonstrated. Similarly, the striatum has been demonstrated to be involved in pain processing (Hagelberg et al., 2004; Pertovaara and Wei, 2008) and abnormalities in somatosensorial (de Tommaso et al., 2001) and

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nociceptive (de Tommaso et al., 2011) responses have been detected in HD patients.

Striatum exerts a balancing effect on pain hypersensitivity at spinal and trigeminal level, via both ipsilateral adrenal dopaminergic descending inhibitory projections and GABAergic descending facilitatory projections (Pertovaara and Wei, 2008). In this sense, previous studies account for an inhibitory role of the striatum on nociceptive specific (NS) and wide dynamic range (WDR) neurons mediating trigeminal nociceptive responses, without modifying the excitability of the motor neurons (Belforte et al., 2001 and Belforte and Pazo, 2005).

One of the most typical abnormalities resulting from pain processing dysfunction is the abnormal temporal summation of pain stimuli. In previous works we demonstrated that abnormalities in temporal processing of pain can be detected in several pain-related neurological disorders such as PD during both early and advanced phase of the disease (Perrotta et al., 2011a) and episodic and chronic form of migraine (Perrotta et al., 2010 and Perrotta et al., 2011b).

In humans, the temporal summation of painful stimuli represents the counterpart of the "wind-up" phenomenon in animals (Price, 1972; Arendt-Nielsen et al., 1994; for review see Sandrini et al., 2005) which is driven by the activity of the WDR neurons (Woolf, 1996). The temporal summation of pain develops in parallel with the temporal summation of the nociceptive withdrawal reflex (NWR) and, in particular, the temporal summation threshold (TST) of the NWR has been demonstrated to be a sensitive tool for exploring both the physiological and pathophysiological mechanisms in spinal cord pain processing (Serrao et al., 2004; Perrotta et al., 2010 and Perrotta et al., 2011a,b) and the functional integrity of descending pathways involved in the supraspinal control of pain such as the diffuse noxious inhibitory control (DNIC) (Serrao et al., 2004; Perrotta et al., 2010). As DNIC acts via spinal-bulbo-spinal adrenergic loop mediated through antinociceptive structures such as periaqueductal gray (Millan, 2002), we hypothesized that the study of the NWR TST and the functional activity of the DNIC could be suitable to evaluate the functional activity of the pain system in the HD.

2. Methods

The study was approved by the local Ethics Committee and was carried out following the guidelines for proper human research conduct in accordance with the Helsinki Declaration of 1975 as revised in 2000 and all the participants gave their written consent.

2.1. Study population

2.1.1. Patients

Nineteen genetically confirmed HD patients (8 female, 11 male; mean age 49.3 ± 9.0 years; range 35–66 years) with clinical duration between 1 and 13 years were enrolled at outpatient clinic for diagnosis and therapy of chronic disease, department of Neurology, University of Bari "Aldo Moro".

Global motor disability was evaluated by means of motor section of Unified Huntington's disease Rating Scales (UHDRS) (Huntington Study Group, 1996), cognitive impairment by Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and cognitive section of UHDRS and functional impairment and stage of illness by Total Functional Capacity (TFC) scale (Shoulson and Fahn, 1979). Patients assuming neuroleptics continued the treatment, the other patients started the treatment after neurophysiological evaluation. Exclusion criteria were: cognitive impairment (MMSE < 24), functional impairment (TFC < 5), severe depression (Beck Depression Inventory > 18) (Beck et al., 1961) and motor section of UHDRS > 60, in order to minimize the influence of chronic movements on the motor responses; current use of anti-depressant medications or analgesics; clinical or instrumental evidence of any central or peripheral disease potentially causing sensory impairment, including nerve conduction studies of motor and sensory nerves; fibromyalgia, neuropathic pain, complex regional pain syndrome (Wolfe et al., 1990; Bruehl et al., 1999; Cruccu et al., 2004) and other pain conditions (Merksey and Bogduk, 1994). All patients' individual demographic and clinical characteristics are reported in Table 1.

2.1.2. Healthy subjects

Seventeen, age and sex matched (8 female, 9 male; mean age 47 ± 6.7 years; range 27–61 years), healthy individuals, without neurological disorders or a clinical history (including family history) of neurological disorders, were recruited as the control group.

2.2. Nociceptive Withdrawal Reflex Measurements

2.2.1. Nociceptive Withdrawal Reflex

The NWR from the right lower limb was investigated according to a validated method (Arendt-Nielsen et al., 1994; Sandrini et al., 2005).

In particular, female patients and controls were matched for cycle phases (follicular phase) in order to minimize the pain modulation across the menstrual cycle (Sandrini et al., 2005), and all the subjects were tested between 09.00 and 11.00 to minimize the effect of diurnal variation (Sandrini et al., 2005). Before formal measurements were started, the subjects underwent training to familiarize them with the pain threshold assessment procedure.

The subjects were seated comfortably in a quiet room at constant temperature (23 ± 2 °C). Their lower limbs were positioned to ensure complete muscle relaxation (knee flexed at 130° and ankle at 90°).

The sural nerve was stimulated percutaneously via a pair of standard surface electrodes (Ag/AgCl) applied to degreased skin behind the right lateral malleolus. The transcutaneous electrical stimulus consisted of a constant current pulse train of five individual 1-ms pulses delivered at 200 Hz (equal to an inter-stimulus interval of 4 ms), randomly applied every 25–40 s. Electromyographic reflex responses were recorded from the capitis brevis of the biceps femoris via surface electrodes (Ag/AgCl). The filter band-pass setting was between 3 Hz and 3 kHz.

The analysis time was 300 ms, with the sensitivity was set at 100 μV. Each response was full-wave rectified and integrated in the 80–130 ms post-stimulus interval (Sandrini et al., 2005) (Electric Stimulator Energy Light, Micromed System Plus Micromed, Mogliano Veneto, Italy).

The staircase method was used to evaluate the NWR threshold (Th), defined as the stimulation intensity generating stable reflex responses with an amplitude exceeding 20 μV for more than10 ms in the time interval 80–130 ms over five stimuli.

The stimulation intensity was fixed at 1.2 × Th; five reflex responses were recorded and the mean NWR area under the curve (Area) was computed using a computerized method.

The subjects rated the psychophysical pain sensation for each stimulus on an 11-point numerical rating scale (NRS), graded from 0 = no pain to 10 = unbearable pain.

The first recording of each session was discarded in an attempt to reduce the influence of the startle reaction.

2.2.2. Temporal summation of the Nociceptive Withdrawal Reflex

The sural nerve was stimulated using a constant current pulse train of five individual 1-ms pulses delivered at 200 Hz repeated five times at a frequency of 2 Hz, as previously described (Arendt-Nielsen et al., 1994; Serrao et al., 2004; Sandrini et al., 2005). The current intensity was increased (in 1 mA steps) from