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Deficient median nerve prepulse inhibition of the blink reflex in cervical dystonia ☆

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HIGHLIGHTS

- Patients with cervical dystonia have less prepulse R2 inhibition than healthy subjects.
- The absence of a sensory trick leads to the more pronounced reduction of prepulse R2 inhibition.
- The modulatory effects of sensory inputs are lost in the absence of a sensory trick.

ABSTRACT

Objective: We analyzed prepulse inhibition (PPI) of the blink reflex (BR) in patients with cervical dystonia (CD) to examine the sensory modulation of the motor system.
Methods: This study enrolled 22 consecutive patients with idiopathic CD and 25 age- and gender-matched healthy subjects. Prepulse inhibition of the BR was recorded after stimulating the median nerve at the wrist using an electrical stimulus twice at a perception threshold 100 ms before a test stimulus to the supraorbital nerve.
Results: The R2 area and amplitude were significantly reduced and the R2 latency delayed after the conditioned stimulus in patients with CD. The R1 latency and amplitude did not differ between trials in patients with CD. In healthy subjects, the R1 amplitude was higher, whereas the R2 latency was delayed and the R2 amplitude and area were reduced after the conditioned stimulus. However, there was significantly less R2 and R2c area suppression in patients compared with healthy subjects. ANOVA showed that reduction of R2 area after conditioned stimulus ($F = 6.620$, $p = 0.003$) and percentage change of R2 area ($F = 5.217$, $p = 0.009$) were lower in patients with and without sensory tricks compared with healthy subjects, whereas the reduction in PPI was pronounced in patients without a sensory trick compared with healthy subjects.
Conclusions: Patients with CD show significantly less prepulse R2 inhibition than healthy subjects, but this occurred without R1 facilitation. The absence of a sensory trick leads to the more pronounced reduction of PPI.
Significance: The modulatory effects of sensory inputs are lost in patients with CD without sensory tricks.

1. Introduction

Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both (Albanese et al., 2013). Cervical dystonia (CD) is a focal dystonia that affects the muscles of the neck and, sometimes, the shoulders. It typically starts in adulthood and may be accompanied by jerky movements of the head and neck. Electrophysiological studies have suggested that decreased inhibi-

Abbreviations: BR, blink reflex; CD, cervical dystonia; ISI, interstimulus interval; MRI, magnetic resonance imaging; PPTN, pedunculopontine tegmental nucleus; PPI, prepulse inhibition; STN, subthalamic nucleus; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

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tion, sensory dysfunction, and abnormal plasticity play roles in the pathophysiology of dystonia (Quartarone and Hallett, 2013). Patients with craniocervical dystonia showed abnormalities of the interneurons mediating exteroceptive reflexes, and these changes were outside the systems controlling the muscles with dystonia (Carella et al., 1994). The probability and magnitude of the auditory startle response were reduced in CD, although the prolonged electromyographic activity after the proper startle response suggested brainstem dysfunction (Müller et al., 2003).

A typical finding of CD is the "sensory trick," which is a reduction in involuntary contraction to a light touch (Albanese et al., 2013; Kagi et al., 2013). Disinhibition of the somatosensory cortex has also been demonstrated in CD (Siggelkow et al., 2002; Kanovský et al., 2003). Therefore, CD is now considered a disorder of sensorimotor gating that probably causes input–output mismatch in specific motor programs (Abbruzzese and Berardelli, 2003; Hallett, 1995; Stamelou et al., 2012).

Prepulse inhibition (PPI) is a neurophysiological method defined as the inhibition of a reflex response caused by applying a subthreshold stimulus before the test stimulus (Graham, 1975; Hoffman and Ison, 1980; Valls-Sole et al., 1999). Prepulse inhibition of the blink reflex (BR) leads to inhibition of the R2 magnitude, whereas a short interstimulus interval (ISI) increases the magnitude of R1 (prepulse facilitation) (Boelhouwer et al., 1991; Ison et al., 1990; Rossi and Scarpini, 1992). The neural correlates of PPI are theorized to be a network between the basal ganglia and brainstem reticular formation, probably including the pedunculopontine tegmental nucleus (PPTN) (Koch et al., 1993; Saitoh et al., 1987; Swerdlow and Geyer, 1993). The PPI has been studied in patients with blepharospasm in whom the PPI was reduced particularly in patients without sensory tricks (Gómez-Wong et al., 1998).

We analyzed the PPI of the BR in a group of patients with CD, because CD is a disorder of sensorimotor integration and PPI is an electrophysiological method used to determine the sensory modulation of motor systems.

2. Subjects and methods

2.1. Subjects

The study enrolled 22 consecutive patients who were seen in our movement disorders outpatient clinic with a diagnosis of idiopathic CD and because the influence of age and gender on PPI of the BR is known, 25 age- and gender-matched healthy subjects (Kofler et al., 2013). Secondary causes of dystonia were excluded in all patients based on history, laboratory investigations, and cranial magnetic resonance imaging (MRI). All patients were assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Electrophysiological assessments were performed in drug-naïve patients or at least 3 months after the last botulinum toxin administration when the complaints reached a maximum level. The study excluded patients who had involuntary contractions of the facial muscles and those who had their facial muscles treated with botulinum toxin.

The study was approved by the Institutional Review Board, and all participants provided informed consent.

2.2. Methods

The electrophysiological recordings were performed using Ag–AgCl surface electromyography recording electrodes (Neuropack Σ-MEB-5504K, Nihon Kohden Corporation, Tokyo, Japan), according to standard techniques.

2.2.1. Blink reflex

The active electrode was placed on the lower eyelid, the reference electrode was placed on the lateral orbital margin, and the ground electrode was placed on the forehead. The supraorbital nerve was stimulated at the supraorbital margin percutaneously. The duration of the electrical stimulus was 0.2 ms, and its intensity was three times the perception threshold (8–14 mA). Five responses were recorded at random intervals of at least 20 s. The reflex response was defined as time-locked deflection with an amplitude of at least 50 μV compared with baseline. The analysis time was 20–30 ms/div, and the sensitivity was 50–200 μV. The filter settings were 3 kHz high-cut and 20 Hz low-cut.

2.2.2. Prepulse inhibition

The median nerve was stimulated using an electrical stimulus of 0.2 ms in duration at two to three times the intensity of the perception threshold; this occurred 100 ms before the test stimulus to the supraorbital nerve. The electrode positioning, filter settings, and sensitivity were the same as for the standard BR investigation. The analysis time was 20–30 ms/div for the investigations. Six trials were performed with at least 10 s between two consecutive stimuli.

2.3. Statistical analysis

Following supraorbital nerve stimulation (test stimulus) and preceding median nerve stimulation/supraorbital nerve stimulation (conditioned stimulus), the onset latencies and peak-to-peak amplitudes of the R1 and R2 responses were measured using cursors. For the PPI analysis, six responses were averaged and rectified. Cursors were placed from the onset to the end of the response, and the R2 area was calculated automatically. The percentage change in the R2 area was calculated as the [R2 area at ISI 100 ms (conditioned stimulus)]/[R2 area at baseline (test stimulus)] × 100.

The data were analyzed using the SPSS 15 statistical package (SPSS, Chicago, IL, USA).

Age, gender, and prepulse stimulus intensity were compared between patients and healthy subjects using the independent-samples *t*-test for quantitative data and the chi-square test for qualitative data with the Bonferroni correction. The TWSTRS score was presented as the mean ± SD, whereas use of botulinum toxin and presence of a sensory trick were presented as the percentage of patients.

The R1/R2 latencies and amplitudes and R2 areas obtained after the test stimuli and the percentage of suppression after the conditioned stimuli were compared between patients with CD and healthy subjects using the Mann–Whitney *U*-test.

The correlation between the TWSTRS scores and conditioned/test R2 area was analyzed using Pearson correlation analysis.

The R1/R2 latencies and amplitudes and R2 areas at baseline and ISI of 100 ms were compared separately within groups of patients with CD and healthy subjects using the Wilcoxon test. The same analysis was repeated by dichotomizing the patient group based on the presence of a sensory trick: patients with and without a sensory trick. We used presence and absence of sensory trick as a grouping factor. The followings were compared among the two groups and healthy subjects using analysis of variance (ANOVA): TWSTRS scores, test R2 area, and conditioned R2 area/test R2 area. *Post-hoc* analysis was performed using Tukey's test.

A p-value $\leqslant 0.05$ was considered significant.

3. Results

The mean ages of the patient group and healthy subjects were 38.1 ± 9.4 and 37.3 ± 10.6 years, respectively ($p = 0.783$). The