Sensory Modulation of the Blink Reflex in Patients With Blepharospasm

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Objective: To measure the effects of a prepulse stimulus on the blink reflex responses elicited by an electrical stimulation of the supraorbital nerve in patients with blepharospasm with and without an effective sensory trick.

Design: Blink reflexes to supraorbital nerve stimulation were preceded in test trials by a prepulse electrical stimulus to the third finger at various leading intervals.

Setting: Ambulatory patients were treated regularly with botulinum toxin in the Neurology Department of the Hospital Clinic in Barcelona, Spain.

Subjects: Seventeen patients with dystonic blepharospasm and 11 age-matched control subjects. Eight of the patients with dystonic blepharospasm used a sensory trick to alleviate spasms and 9 did not.

Main Outcome Measures: We measured amplitude of R1 and area of R2 responses elicited by the supraorbital electrical stimulus and determined the percentage of facilitation or inhibition induced by the prepulse.

Results: Prepulse facilitation occurred in the R1 response at intervals of 60 to 100 milliseconds and was normal in all patients. Prepulse inhibition occurred in the R2 response at intervals between 50 and 200 milliseconds and was abnormally reduced in 11 patients (64.7%), including all 9 patients who did not use a sensory trick and 2 of the 8 patients who did use a sensory trick. There was a positive correlation between absence of sensory trick and abnormality of the prepulse effects ($\chi^2 = 23.8; P < .001$).

Conclusions: Prepulse inhibition of the trigemino-facial reflex is abnormal in a percentage of patients with blepharospasm, and this abnormality occurs more frequently in patients who do not use a sensory trick. This sensory derangement may contribute to the maintenance of the dystonic spasms by reducing the amount of physiological gating from peripheral nerve inputs on trigemino-facial reflexes.

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PATIENTS WITH dystonic blepharospasm exhibit an abnormal excitability of the blink reflex to paired electrical stimulation of the supraorbital nerve. Such a dysfunction may result from abnormalities in the control exerted by the basal ganglia on the excitability of the brainstem interneurons of the trigemino-facial circuit. Because of the integrative function of the brainstem on sensory inputs from many nerves, it is conceivable that the abnormal control exerted by the basal ganglia also affects the sensory inputs carried by nerve afferents of the upper limbs.

Some patients with dystonia exhibit a trick or geste antagonistique, which they use to transiently alleviate the spasms. Although little is known regarding the physiological features of the sensory trick, it is likely that its effects are related to a gating mechanism by which the afferent inputs generated from the trick interfere with abnormally functioning reflex circuits. A gating mechanism is similarly implied in the physiological characteristics of the prepulse effects on the blink reflex. Therefore, we hypothesized that patients with dystonic blepharospasm could have an abnormally reduced prepulse inhibition, and that such an abnormality could be associated with an ineffective or inexistent sensory trick.

RESULTS

CLINICAL ASPECTS

The clinical characteristics of all patients examined are summarized in Table 1. All patients exhibited a transient improvement with botulinum toxin injections that had remitted by the time of the study. Of 8 patients who used a sensory trick, 3 rated it as very effective (patients 2, 4, and 6), and 5 rated it as poor (Table 1).
SUBJECTS AND METHODS

SUBJECTS

The study included 17 patients (15 men and 2 women; age range, 38–82 years). All patients had dystonic blepharospasm, and 5 patients also had signs of dystonia in the lower face (cranial dystonia). We excluded patients who were receiving medications such as dopamine antagonists or tetrabenazine. No patient was diagnosed as having schizophrenia or manic depression. We also examined 11 patients who were periodically treated with botulinum toxin injections. All patients had dystonic blepharospasm, and 5 patients also had signs of dystonia in the lower face (cranial dystonia). We defined a sensory trick as the self-application of a contact stimulus on specific sites in the face that induced a transient relief of the dystonic spasms not in proportion to the intensity of the stimulus and not explained by the induction of a movement antagonistic to the dystonic posture or movement. All patients were requested to rate their sensory tricks as very effective, poor, or absent. The severity of the dystonic features was assessed using the Scott modified scale. All patients were periodically treated with botulinum toxin injections. The studies herein were performed between 3 and 4 months after the patients’ dystonic spasms had resumed following transient relief from one of these treatment sessions.

RECORDING AND STIMULATION

Orbicularis oculi responses were recorded with a pair of surface recording electrodes placed 3 cm apart at the lower eyelid. Electrical stimulation of the supraorbital nerve was delivered with a pair of surface electrodes, with the cathode placed at the supraorbital notch and the anode placed over the forehead, at an intensity that gave rise to a stable R2 response in repeated single tests. The electrical stimulus used as a prepulse was delivered with ring electrodes to the digital nerves of the third finger of the right hand at an intensity between 1.5 and 3.0 times the subject’s sensory perception threshold. We made sure in all subjects that the prepulse stimulus was insufficient to elicit a response in the orbicularis oculi.

All electromyographic recordings were made with an electromyograph (Neuropack 8, Nihon-Kohden, Tokyo, Japan) with a band pass frequency filter set at 50 to 10,000 Hz.

PROCEDURE

The subjects were instructed to lie on an examination bed in a room at moderate temperature. We randomly conducted 3 types of trials involving different stimulus combinations: the supraorbital nerve stimulus alone, the prepulse stimulus alone, and the prepulse stimulus preceding the supraorbital nerve stimulus by a variable interstimulus time interval (ISI). The ISIs used for all subjects were 40, 50, 60, 70, 80, 90, and 200 milliseconds. For a few patients we also used ISIs of 10, 20, 30, 125, 150, 175, 300, and 400 milliseconds. All recordings were made within 500 milliseconds, in which time the prepulse stimulus was presented with a delay of 100 milliseconds from onset of the trace.

We also examined the blink reflex excitability recovery curve by applying paired (conditioning and test) stimuli to the supraorbital nerve, separated by ISIs ranging from 100 to 1000 milliseconds in steps of 100 milliseconds. At least 2 trials were conducted at each ISI, with a period of rest of at least 10 seconds between each trial. The intensity of the electrical stimulation of the supraorbital nerve was the same as that used in the previous experiment.

DATA REDUCTION AND ANALYSIS

Statistical analysis was performed separately for control subjects, patients who used a sensory trick (including those who rated the sensory trick as either very effective or poor), and patients who did not use a sensory trick. For all subjects and recordings, we measured the peak amplitude of the R1 and the area (peak amplitude × duration) of the R2 response obtained during each trial. For each group of subjects, we normalized the data by assigning the value of 100% to the amplitude of the R1 and area of the R2 elicited by the supraorbital nerve stimuli in trials without the prepulse (control values), and represented the data obtained in trials with prepulse (test trials) as the percentage of the control values. To determine the statistical significance of the effects induced by the prepulse stimulus at each of the ISIs tested, we compared the mean percentages of R1 facilitation and R2 inhibition with the control values using repeated measures analysis of variance (ANOVA). For control subjects, we determined the 2 ISIs at which the effects induced by the prepulse stimulus were larger for R1 and R2, and used the data gathered from those ISIs for statistical comparison (1-way ANOVA) between control subjects and each group of patients. For analysis of the results for single individuals, we considered that the prepulse-induced facilitation of R1 and inhibition of R2 were normal when the percentage change was within the mean ± 2 SDs of that obtained in the group of control subjects in at least 2 ISIs between 40 and 100 milliseconds. We used the χ² test for non-parametric analysis of the data.

Using the blink reflex excitability recovery curve, we determined the percentage of recovery by dividing the area of the R2 response to the test stimulus by that of the R2 response to the conditioning stimulus at all ISIs tested. For analysis of the results for single individuals, we considered that the excitability recovery curve was abnormal when the percentage of recovery was larger than 20% at an ISI of 200 milliseconds or 80% at an ISI of 1000 milliseconds. For a statistical comparison between groups of subjects, we determined the shortest ISI at which the percentage of recovery was at least 10%. Statistical comparison was performed with 1-way ANOVA.
The blink reflex excitability recovery curve showed an abnormally enhanced recovery of the R2 to the test stimulus in all patients (100%) who did not use a sensory trick and in 6 (75%) of the 8 patients who did.

**PREPULSE EFFECTS**

The digital nerve electrical stimulus (prepulse stimulus) induced effects on the responses elicited by the electrical stimulation of the supraorbital nerve in all control subjects and in approximately 50% of the patients. Some examples of these effects seen in selected patients are shown in Figure 1. In control subjects, the R1 was facilitated at ISIs between 60 and 100 milliseconds, with the peak of the effect at an ISI of 80 milliseconds (Figure 2, A). Facilitation of the R1 was also observed in both patient groups, those with and without a sensory trick, with no significant differences found in the comparison between patients of either group and control subjects (Figure 2, B and C). The R2 was significantly inhibited in control subjects at all ISIs between 50 and 200 milliseconds, with the peak of the effect at an ISI of 90 milliseconds (Figure 3, A). The results for all patients were not uniform. Patients who used a sensory trick showed inhibition of R2 in a percentage that was not different from that observed in control subjects at any of the ISIs tested (Figure 3, B). Conversely, patients who did not use a sensory trick had significantly less inhibition than control subjects or patients who used a sensory trick at all ISIs between 50 and 100 milliseconds (Figure 3, C).
The presence of a sensory trick, either effective or poor, and a sensory trick (patients 1 and 7) rated their sensory trick as 6, and 8) (Table 1). The 2 remaining patients who used a sensory trick had normal prepulse inhibition, while those who did not had no inhibition.

Among the electrophysiological data, the only significant difference was found in the percentage of prepulse inhibition of the R2 response. Patients who used a sensory trick had normal prepulse inhibition, while those with dystonic blepharospasm are able to transiently reduce the intensity of the spasms and carry on with their tasks with less interference from the unwanted muscular activity.5-8 In these patients, the afferent volley generated by the sensory trick may modulate the activity in the trigeminothalamic pathways. The abnormalities in the central processing of sensory inputs in patients with various forms of dystonia is one expression of the abnormal processing of trigeminal sensory inputs.9,13-17 We and others have previously shown that the prepulse effects induced in the trigeminofacial reflexes by volleys generated in the peripheral nervous system take place at the trigeminal afferents.9,16,17 Therefore, the abnormal prepulse inhibition found in this study is consistent with a dysfunction in the sensory pathways.

We examined the function of sensory processing mechanisms in patients with dystonic blepharospasm using the test of prepulse inhibition, or modification of the blink reflex.6,13-15 The main findings of this study are as follows: (1) The prepulse inhibition of the R2 was abnormal in 11 (64.7%) of 17 patients with blepharospasm. (2) There was a significant correlation between abnormally reduced prepulse inhibition and absence of a sensory trick. (3) There was a weak correlation between reduced prepulse inhibition and the enhanced blink reflex excitability recovery curve, although the latter was abnormal in a larger proportion of patients.

Our findings suggest that patients with dystonic blepharospasm might have abnormalities in sensorimotor gating mechanisms. It has recently been suggested that the primary cause of dystonia can be an abnormality in the central processing of sensory inputs.10,19 It may be that the abnormal blink reflex excitability recovery curve found in patients with various forms of dystonia is one expression of the abnormal processing of trigeminal sensory inputs. A widely accepted method for testing central nervous system modulation of sensory inputs is prepulse inhibition.13-15 We and others have previously shown that the prepulse effects induced in the trigeminothalamic reflexes by volleys generated in the peripheral nervous system take place at the trigeminal afferents.9,16,17 Therefore, the abnormal prepulse inhibition found in this study is consistent with a dysfunction in the sensory pathways.

By applying a contact stimulus to a specific site, patients with dystonic blepharospasm are able to transiently reduce the intensity of the spasms and carry on with their tasks with less interference from the unwanted muscular activity.5-8 In these patients, the afferent volley generated by the sensory trick may modulate the activity in the trigeminothalamic circuit. Similar explanations have been given by previous authors reporting examples of the effectiveness of sensory tricks. In pa-

**Correlation Between Sensory Trick and Prepulse Inhibition**

There were no differences in the clinical aspects of patients who did and did not use a sensory trick (Table 2). Among the electrophysiological data, the only significant difference was found in the percentage of prepulse inhibition of the R2 response. Patients who used a sensory trick had normal prepulse inhibition, while those who did not had no inhibition.

Using the criteria described in the “Methods” section to assess whether the prepulse effects were normal in a given individual, we found that all subjects fell within the normal range for both the R1 facilitation and the R2 inhibition. Six patients had normal prepulse inhibition, all of whom exhibited a sensory trick (patients 2, 3, 4, 5, 6, and 8) (Table 1). The 2 remaining patients who used a sensory trick (patients 1 and 7) rated their sensory trick as poor. There was a significant correlation between the presence of a sensory trick, either effective or poor, and normal prepulse inhibition ($\chi^2 = 23.8; P < .001$).
tients with cervical dystonia, Cleeeland\textsuperscript{20} reports a reduction of the spasms with repeated electrical stimulation of the fingers, and Leis et al\textsuperscript{21} report the beneficial effects of vibration applied to selected neck muscles. In patients with forearm dystonia, Kaji et al\textsuperscript{19} report the effects of skin contact on vibration-induced abnormal posturing. Our finding of a significant correlation between sensory tricks and normal prepulse inhibition suggests that the beneficial effect of the sensory trick is actually related to the preservation of a functionally active physiological mechanism of prepulse inhibition.

Not all patients with dystonia have the benefit of a sensory trick, and some report the loss of an effective sensory trick. This observation, together with the correlation between sensory trick and functional prepulse inhibition, suggests that abnormalities in sensorimotor gating mechanisms are the consequence rather than the cause of the dystonia. The unwanted muscle activity that is characteristic of the dystonic spasms may cause abnormal sensory volleys to reach central nervous system circuits associated with dystonia. Such an oversized input may induce an abnormal overactivity in spinal or brainstem interneurons, producing changes in neuronal metabolism. Continuous overactivity may induce segmental reorganization in neuronal connectivity, which could lead to the stabilization of abnormal reflex circuits and the loss of previous modulatory effects from sensory inputs.

Reflex responses such as the blink reflex and the startle reaction are likely protective mechanisms. However, overactivity of the reflex circuits leading to such responses can have a deleterious effect. Habituation and sensory gating constitute probably the most basic strategies used by the central nervous system to limit the number of responses in a certain period. Failure of habituation and abnormality in sensory gating mechanisms can be partly responsible for the enhanced muscular activity seen in some patients with movement disorders. The mechanisms of sensory gating are likely amenable to adaptation and learning, which brings up therapeutic possibilities.\textsuperscript{20-22} It might be helpful to recognize patients with dystonia and normal prepulse inhibition, who may be more likely to benefit from treatments devised to reinforce the physiological mechanisms of sensory modulation.

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