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Letter to the Editor

Unravelling mechanisms of altered modulation of trigemino-facial circuits in blepharospasm

Blepharospasm (BSP) is an adult onset focal dystonia characterized by stereotyped, bilateral, and synchronous spasms of the orbicularis oculi muscles (Defazio et al., 2017). The neurophysiological hallmark of BSP is an enhanced excitability of blink reflex circuits in the brainstem, as evaluated by the recovery cycle of the R2 component of the blink reflex (Defazio et al., 2017), which is possibly due to a lack of inhibition from basal ganglia structures.

Using the Pre-Pulse Inhibition (PPI) protocol, which consists of delivering an electrical stimulus to the upper limb shortly before an electrical stimulus delivered to the supraorbital nerve for blink reflex response, an earlier study showed that blink reflex response was less inhibited in BSP patients than in healthy subjects (Gomez-Wong et al.,1998). The authors did not find a significant correlation between reduced PPI and the enhanced blink reflex excitability recovery curve and suggested that this result was probably due to the limited sample size of patients studied. Since there is an altered processing of sensory information in BSP (Conte et al., 2019) as evaluated by the somatosensory temporal discrimination threshold (STDT), it is possible that abnormal sensory processing may also play a role in the reduced PPI. For this reason, we investigated the R2 recovery cycle of the blink reflex, PPI, and the STDT in a group of patients with BSP.

We studied 24 patients with BSP (M/F:10/14; mean age: 65.710 years; disease duration: 11.74years) and 24 age-matched healthy controls (M/F:9/15; mean age: 63.08years). Patients were consecutively enrolled at the Movement Disorder Clinic, Department of Human Neurosciences, Sapienza University of Rome, Italy. BSP was diagnosed according to validated diagnostic criteria (Defazio et al., 2017). Clinical and neurophysiological assessments were performed at least four months after the last botulinum toxin injection. The experimental procedure was approved by the ethics committee of Sapienza University of Rome and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant. All patients were video recorded to determine the severity of BSP according to the Blepharospasm Severity Rating Scale (BSRS) (Defazio et al., 2015). Presence of ocular symptoms, sensory trick, and disease duration were recorded.

The blink reflex recovery cycle was studied according to a previous experimental procedure (Conte et al., 2017). Briefly, paired square-wave pulses were delivered to the supraorbital nerve through surface electrodes at Interstimulus Intervals (ISIs) of 250, 500, and 1000ms. Twenty trials for paired-pulse stimulation were performed with an inter-trial interval of 4060s. The R2 response area was calculated for each block using Signal software (Cambridge Electronic Design Limited, Milton, Cambridge, U.K.). We then calculated the ratio between the area of the conditioned/conditioning R2 response. Mean percentage variations of R2 were thus obtained at ISIs of 250, 500, and 1000ms and entered into data analysis.

We evaluated PPI according to previous experimental procedures (Gomez-Wong et al.,1998) by delivering an electrical stimulus to the median nerve on the right wrist 100ms before an electrical stimulus delivered to the supraorbital nerve to elicit the R2 blink reflex. Ten trials were performed with at least 10s between each trial. PPI was expressed as the ratio of the R2 area component of the blink reflex conditioned by the peripheral median nerve stimulation and the unconditioned R2 area component of the blink reflex test.

For STDT testing (Conte et al., 2017), paired electrical stimuli were delivered to the volar surface of the right index finger. The interstimulus interval of the paired stimuli was progressively increased in 10-ms steps. The STDT was defined as the shortest of three consecutive ISIs at which the subject recognized the stimuli as separate in time.

ANOVA was used to compare the blink reflex recovery cycle, PPI, and the STDT between patients and healthy subjects. Using a partial correlation coefficient (controlled for group and age) we evaluated the relationship between PPI changes and blink reflex excitability and between PPI and the STDT in patients and healthy subjects. A P value<0.05 indicated statistical significance.

BSP patients had a mean BSRS score of 8.44. Thirteen BSP patients had sensory trick touching the face whereas eighteen BSP patients reported ocular symptoms.

Between group repeated measures ANOVA showed significant factors GROUP ($F=53.3$, $p<0.001$) and ISI ($F=78.9$, $p<0.001$), and a significant GROUPæISI interaction ($F=3.8$, $p=0.02$). R2 inhibition was reduced in BSP patients as compared to healthy subjects at all ISIs tested (250ms: $p<0.001$, 500ms: $p<0.001$; 1000ms: $p=0.001$). PPI was significantly reduced ($F=22.1$, $p<0.001$) and STDT was increased in BSP patients as compared with healthy subjects ($F=44.9$; $p<0.001$). The partial correlation coefficient disclosed significant relationships between abnormal PPI and the degree of excitability of blink reflex recovery cycle at shorter ISIs (250ms: $p=0.003$; 500ms: $p=0.04$) (Fig. 1), but no relationship was found with STDT values ($p=0.64$).

In the present study we found that abnormalities in the R2 recovery cycle of the blink reflex did not correlate with an altered processing of sensory information as evaluated by the STDT. However, our results showed that PPI was correlated with blink reflex recovery cycle abnormalities. The correlation we found suggests that the more hyperexcitable the trigemino-facial reflex, the lesser the likelihood that sensory input arriving shortly (100ms) before blink reflex activation will inhibit eyelid closure.

We conclude that in BSP there is decreased inhibition of brainstem interneurons mediating the blink reflex after stimulation of the supraorbital nerve, and also after stimulation of the peripheral nerve in the upper limbs. This decreased inhibition of brainstem

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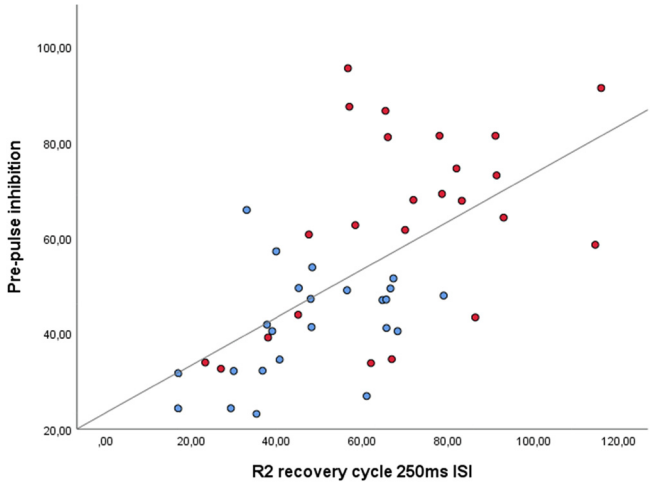

Fig. 1. Correlation between Pre-pulse Inhibition (PPI) and the R2 recovery cycle of the blink reflex at 250 ms Interstimulus Interval (ISI). Both variables are expressed as percentage changes. Blue dots indicate healthy controls, red dots are the BSP patients.

interneurons is independent of the abnormal sensory input processing, as evaluated by the STDT.

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Declaration of Competing Interest

None.

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