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Effects of a selective serotonin reuptake inhibitor escitalopram on the cutaneous silent period: A randomized controlled study in healthy volunteers

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HIGHLIGHTS

- The cutaneous silent period (CSP) is a spinal noxious inhibitory reflex.
- Escitalopram shows a selective action in inhibiting serotonin reuptake.
- Escitalopram increases CSP duration without affecting subjective pain sensation.
- We provide evidence for monoaminergic system involvement in the generation of CSP.

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ABSTRACT

The cutaneous silent period (CSP) involves a transient inhibition of the electromyographic (EMG) activity in the hand muscles induced by a painful electrical stimulation of the digital nerves. The neurotransmitters potentially involved in mediating the CSP have not been completely elucidated thus far. However, few studies suggest that the monoaminergic system may play a role in the CSP. We elicited CSPs in the first dorsal interosseous muscle of the right hand before and 3 h after administration of a single oral dose of the selective serotonin reuptake inhibitor escitalopram (20 mg) or placebo. The two experimental sessions (drug and placebo) were performed in a random order at ≥1-week intervals. All recordings were numbered anonymously and analysed offline in a blind manner by one investigator. A significant increase in the CSP duration was observed 3 h after escitalopram administration ($p = 0.01$), and no changes were observed in the reflex latency and subjective pain sensation ($p > 0.05$). No significant changes were observed in the CSP duration in subjects who received the placebo (all, $p > 0.05$). Our results indicate that escitalopram increases the central disposition of serotonin and increases the activity of the spinal inhibitory interneurons on the α-motoneurons of the hand muscles. Thus, our results indicate the involvement of the monoaminergic system in controlling the spinal pain mechanisms by supraspinal descending pathways originating from the brainstem neural structures.

The cutaneous silent period (CSP) is a spinal reflex recorded as a temporary pause of voluntary muscle contraction in response to painful cutaneous stimuli [1–3]. Although the CSP has been mainly investigated in the hand muscles, CSP can be evoked in many different muscles of the body [4]. The extensive presence of such a reflex reflects the existence of a powerful spinal interneuronal system, which strongly inhibits the activity of motoneurons for nocifensive responses. The CSP is functionally linked to the nociceptive withdrawal reflex [5]. Both the inhibitory (CSP) and excitatory (withdrawal reflex, WR) responses seem to constitute a complex system aimed at protecting the limb from a potential injury (e.g. retracting the arm and releasing the hand grip from a hot stove) [5]. In addition to a role in nocifensive responses, the CSP similar to the WR, may play a role in motor responses, which can be attributed to

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the fact that the interneuronal network mediating the CSP is, itself, modulated by the transmission of descending motor commands to the target motoneurons [2,4,6].

Thus, considering the information mentioned above, improved understanding of the chemicals involved in the substrate mediating the CSP is important to use drugs that increase or decrease the inhibition of the spinal cord neurons. However, neurotransmitters that mediate the CSP circuitry have not been completely elucidated thus far. Previous studies conducted in healthy subjects indicate that drugs such as opioids (fentanyl) [7], gamma-aminobutyric acid B ($GABA_B$) agonists (baclofen) [8], and histamine antagonists (cetirizine) [9] have no effect on the CSP duration. In contrast, a recent study has shown a marked effect of tramadol on the CSP duration in healthy subjects [10]. Since tramadol is an atypical opioid that also inhibits the reuptake of serotonin and norepinephrine, the monoaminergic system is suggested to play a role in the generation of the CSP. Previous studies on patients with Parkinson disease and restless legs syndrome showed that administration of L-3,4-dihydroxyphenylalanine (L-DOPA) markedly modified the CSP parameters further, which suggests that monoamines may play an important role in the inhibition of spinal transmission in motoneurons.

To elucidate the role of monoaminergic pathways in mediating the CSP in detail, we examined the effects of escitalopram, a selective serotonin reuptake inhibitor, on CSP in a group of healthy subjects in a double-blind, randomized, placebo-controlled study.

We enrolled 23 subjects (14 women and 9 men). Participants were required to have no personal or family history of any medical condition. The average age of the subjects was 31.95 ± 3.8 years, and their body mass index (BMI) was 24.8.

To avoid bias, no drugs, caffeine, or alcoholic drinks were allowed less than 72 h before the recording, and in women, the examination was performed outside of menses (thereby excluding hormone-related effect).

Health conditions were examined before, during, and 15 days after completion of the study.

An initial training session was performed to familiarize the participants with the test mode.

The local research ethics committee approved this study, and all the healthy volunteers participated in this study after giving their written consent and after being thoroughly informed of the potential contraindications of a single dose administration of escitalopram. Moreover, this study was performed according to the guidelines of the Declaration of Helsinki on human experimentation.

The task of the subjects was to achieve an isometric contraction in the first dorsal interosseous muscle against a fixed bar placed above a horizontal plane while a cutaneous electrical stimulus, a square-wave pulse lasting 0.2 ms, was delivered through surface ring electrodes applied around the interphalangeal joints of the fifth digit of their right hand. The intensity of the stimulus used was 20 times the value of the sensory threshold (mean, 4.6 ± 1.8 mA). The level of the isometric contraction was approximately maintained at 50% of the maximum. Five maximal voluntary contractions (MVCs), lasting 6–8 s, were recorded. Then, the subjects performed five isometric contractions, each lasting 6–8 s, at 50% of the MVC, with the aid of EMG acoustic and visual feedback.

Sensitivity was set at 50–1000 μV by using a 30–3000 Hz bandpass. During stimulations, subjects performed a constant contraction of the first dorsal interosseous muscle for about 3 s followed by a 10 s rest to avoid muscle fatigue. This pattern was repeated 10 times, which enabled registration of 10 consecutive CSPs. All traces were rectified and averaged. The duration of the CSP was obtained by measuring the arithmetic difference between the CSP onset and offset latencies, which were recorded when the averaged signal dropped below and returned to above 80% of the baseline electromyographic level (obtained during a 100-ms epoch preceding the stimuli), respectively.

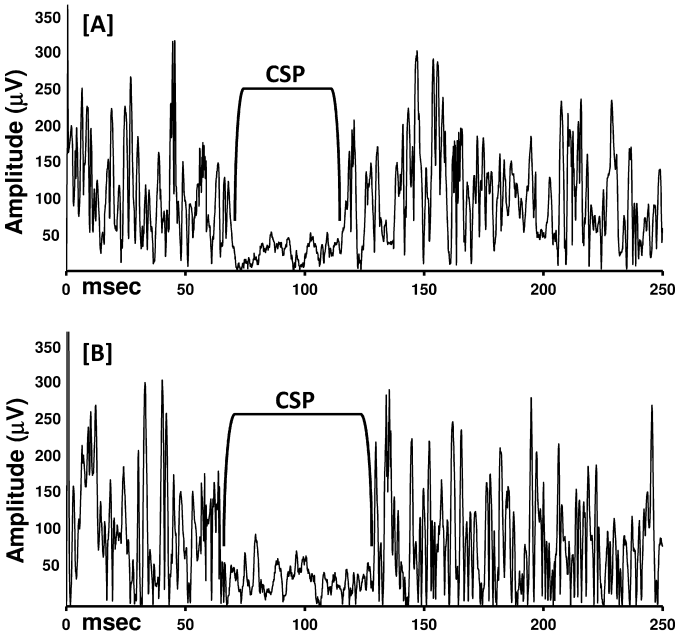

Fig. 1. Illustrative recordings of cutaneous silent period (CSP), before [A] and 3 h after [B] escitalopram administration.

Participants were asked to quantify their perceived pain intensity by indicating a number on an 11-point numerical pain rating scale (11-PNS), graded from 0 = no pain to 10 = worst pain ever.

Room temperature was set at 21–24 °C, and skin temperature was always above 31 °C. The testing started between 9 and 10 AM for all the participants, and all subjects observed a 10-h overnight fast and consumed low-fat meals for the entire study period.

We administered 20 drops of escitalopram (Lundbeck, Italy) oral solution, equivalent to 20 mg/mL of escitalopram base, or an identical-appearing placebo orally. The two recording sessions were performed in random order at ≥7 to ≤10 day intervals by the same investigators. Randomization was conducted using a secure web-based database.

CSP was recorded before (baseline) and at 3 h (at the haematic peak) after escitalopram or placebo administration. Participants, investigators, and clinical centre staff were blinded to treatment assignment. All recordings were numbered anonymously and analysed offline in a blind manner by one investigator. Once the test started, subjects were under observation for 10 h, and vital signs (body temperature, pulse rate, blood pressure, and respiratory rate) were monitored.

Statistical analyses were performed using a dedicated statistical software (SPSS 19.0, Chicago, IL, USA). The changes in the electrophysiological parameters and 11-PNS before and after escitalopram or placebo administration were analysed using Wilcoxon signed-ranks test. Non-parametric Mann–Whitney test was used to compare escitalopram vs. placebo group. For all the tests performed, statistical significance was set at $p < 0.05$.

Escitalopram group included 6 women and 6 men (mean age, 31.8 ± 3.19 years; weight range, 58–75 kg; BMI range, 20.5–27.5). The placebo group included 8 women and 3 men (mean age, 32.11 ± 4.62 years; weight range, 56–74 kg; BMI range, 21.5–27.0).

One subject (woman) in the escitalopram group withdrew from the study because of side effects (nausea/vomiting), and her data were excluded from the analysis.

Examples of CSP recordings before and after escitalopram administration in a representative subject are shown in Fig. 1.