Images in Neurology

Dopamine-Mediated Yawning-Fatigue Syndrome With Specific Recurrent Initiation and Responsiveness to Opioids

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A 59-year-old man presented for care who, for 8 years, had had recurrent attacks of yawning and severe fatigue initiated by relatively mild exercise of his right leg (**Figure**). In 2011, he had a herniation of the L4-5 disc, which affected the right L4 root. Conservative treatment noticeably reduced the sciatic pain on the right side within a few months. However, after this event, he would promptly experience attacks of yawning and fatigue each time he engaged in moderate exercise of the right leg (eg, going upstairs, riding a bicycle, or repeatedly pushing certain weights only with his right leg). Attacks were not associated with a headache or body temperature change, and similar exercises of the other 3 limbs did not provoke yawning and fatigue. Neurological, endocrine, and cardiopulmonary investigations, including brain magnetic resonance imaging, echocardiography, polysomnography, and right-leg electrophysiology, yielded no crucial pathological findings. **Video 1** shows an attack of yawning and fatigue symptoms while walking on a treadmill, immediately after an increase of the incline to 3%.

Video

Yawning rarely occurs as a main feature in neurological disorders. Various neurotransmitter systems interact to regulate yawning,[1] with dopamine playing a key role. Dopamine elicits yawning via the activation of oxytocin production in the hypothalamic paraventricular nucleus, through D3 dopamine receptors and subsequent cholinergic transmission, particularly in the hippocampus.[2] In rats, application of the nonselective dopamine agonist apomorphine increases yawning frequency.[3] Yawning also is an adverse effect of apomorphine use in humans.[4] **Video 2** shows that, under resting conditions, subcutaneous injection of a low dose (2 mg) of apomorphine within a few minutes induced the same clinical symptoms in this patient as were observed at earlier points during exercise of his right leg. Hypothetically, the patient's initial clinical condition with severe sciatic pain in the right leg induced an associative, movement-specific, and recurrent activation of his apparently sensitive hypothalamic dopaminergic system.

Figure. Patient Yawning

Opioid agents seem to inhibit yawning through μ-opioid receptor activation, particularly in the paraventricular nucleus.[2] After subcutaneous injection of the μ-opioid receptor agonist piritramide (3.75 mg), the same exercise on the treadmill as in Video 1 did not trigger yawning and fatigue (**Video 3**). This was the case not only after increase of the treadmill incline to 3% but also after subsequent increases up to 7%, applied stepwise every 5 minutes (Video 3). During similar exercise on the treadmill, the patient's oxygen saturation, heart rate, blood pressure, and body temperature did not change after injection of piritramide compared with the untreated condition (data not shown). The patient has now been successfully treated several times per week by the oral μ-opioid receptor agonist tilidine (50 mg, plus 4 mg of naloxone) before each bout of exercise. Under this treatment regimen, strain of his right leg did not trigger yawning and fatigue. While we are not able to directly assess dopaminergic neurotransmission in corresponding hypothalamic regions, these observations are consistent with the conditioning of an apparently hypersensitive hypothalamic dopaminergic system in the patient. Application of an oral μ-opioid receptor agonist presents a reasonable treatment option for patients with a similar disorder.

ARTICLE INFORMATION

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