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Research report

Dopamine D2-like receptor activation antagonizes long-term depression of orofacial sensorimotor processing in anesthetized mice

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Abstract

Long-term depression (LTD) of orofacial sensorimotor processing recently has been demonstrated in anesthetized mice. Due to the remarkable role of dopamine in central nervous system LTD, the influence of dopamine D2 receptor activation on LTD of the jaw-opening reflex (JOR) was investigated. Electric low-frequency stimulation (LFS, 1 Hz) of the tongue suppressed the JOR integral by 43% for at least 1 h. After systemic administration of the dopamine D2-like receptor agonist quinpirole, LTD was significantly attenuated to 14%. JOR decreased for only about 15 min after LFS according to a short-term depression. Under systemic application of the dopamine D2-like receptor antagonist sulpiride, LTD significantly increased to 64%, again for at least 1 h. Thus, D2-like receptor activation prevented LTD, and D2-like receptor blockade amplified LTD of the reflex. The time course of inhibition may be due to a dopaminergic D2-like receptor mechanism that antagonizes the transfer from short-term into long-term depression. Considering a putative mediation of LTD by the endogenous pain control system, the results correspond to the known inhibitory control of this system by a D2-like receptor mechanism.

Theme: Motor systems and sensorimotor integration
Topic: Spinal cord and brainstem

Keywords: Brainstem; Orofacial; Plasticity; Somatosensory; Trigeminal

1. Introduction

Conditioning electric stimulation of somatosensory afferent nerve fibers induces long-term depression (LTD) of spinal synaptic transmission in-vitro [12,13,25,26]. Recently, LTD could also be demonstrated under in-vivo conditions for brainstem sensorimotor processing by applying the jaw-opening reflex (JOR) in mice [10]. Electric low-frequency stimulation (LFS) of tongue afferents induced sustained decrease of the reflex integral for at least 1 h. The JOR in mice was suggested to be an appropriate model to investigate central mechanisms and pharmacology of synaptic plasticity in the orofacial region in-vivo.

Dopamine plays a major role in modulation and induction of central nervous system LTD. In corticostriatal synapses, dopamine D1-like and D2-like receptor activation interacted synergistically to allow LTD formation in-vitro [6]. Tetanic stimulation of corticostriatal fibers produced LTD in brain slices from wild-type mice but showed the converse in mice lacking dopamine D2 receptors [5]. Excitatory synapses in the nucleus accumbens and the midbrain expressed LTD, but the basic triggering mechanisms differed [28]. Whereas dopamine blocked LTD induction in the midbrain via D2-like receptor activation, LTD of the nucleus accumbens was unaffected. Thus, in-vitro experiments indicated various influences of dopamine on LTD. The present study addressed the hypothesis that LTD of the orofacial JOR in anesthetized mice is under dopaminergic control via D2-like receptors.

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2. Materials and methods

The jaw-opening reflex (JOR) was investigated in 24 adult male Balb/cAnNCrlBR mice (about 12 weeks old; 21 to 26 g). All procedures received institutional approval from the local ethics committees of the University of Erlangen-Nuremberg (ref. no. 621-2531.31-15/01) and the University of Aachen (ref. no. 50.203.2-AC 15, 16/03). The principles of laboratory animal care and use of laboratory animals (European Communities Council Directive of November 24, 1986 (86/609/EEC)) were followed. All efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

A detailed description of anesthesia, surgery, and electrophysiological recording in mice recently has been published [10,11]. Mice were anesthetized by an initial intraperitoneal injection of a 0.5% pentobarbital sodium salt (Sigma-Aldrich, Germany) solution with a dose of 70 mg/kg. The left external jugular vein was catheterized for continuous administration of a 1% methohexital sodium salt solution with a dose of 60 mg/kg/h. A pair of Teflon-coated stainless steel wires (140 μm diameter) was inserted into the right anterior digastric muscle (Dig) to record electromyographic activity (EMG) via a differential amplifier. After tracheotomy, animals were placed in a stereotaxic frame and were artificially respired with a stroke volume of about 0.5 ml and about 180 strokes per minute for the duration of the experiment. The body core temperature was maintained at 37.5 °C, the electrocardiogram (ECG) was recorded. Two stainless steel needle electrodes (150 μm diameter) were longitudinally inserted into the tongue musculature (parallel, 2 mm distance) to apply electric stimuli. Electric test stimulation to evoke the JOR and electric LFS were applied by the same intramuscular tongue electrodes. After surgery and placement of all electrodes, the anesthetized animal had a rest for at least 1 h.

All electric signals (EMG, ECG) were recorded by bioamplifiers and led into a data collection system (CED micro 1401) and a personal computer to compile waveform files using the Signal software program (CED, Cambridge, UK).

The JOR was elicited by rectangular electric pulses of 500 μs duration with a stimulation frequency of 0.1 Hz. The electric threshold of the JOR was determined by applying increasing and decreasing stimulus intensities from 0 to 2 mA in steps of 100 μA. The lowest stimulus intensity that just evoked a reflex response was defined as the JOR threshold (I_{JOR}). Test stimulus intensity was adjusted to 1.5 times the I_{JOR}. The JOR was evoked in blocks of 5 stimuli each. These blocks were repeated every 5 min. After three stable baseline JOR blocks, either the dopamine D2-like receptor antagonist sulpiride (0.1% dilution in isotonic saline; 10 mg/kg; Meresa®, Dolorgiet, Germany) or the dopamine D2-like receptor agonist quinpirole hydrochloride (0.02% dilution in isotonic saline, 10 μg/kg; Eli Lilly, U.S.A.) was systemically administered by intraperitoneal injection. Different drug doses were tested in a preliminary investigation to find appropriate maximum doses of sulpiride and quinpirole that did not affect baseline JOR. After drug administration, three test stimulation blocks were conducted before conditioning electric stimuli were applied (LFS). In control experiments, only LFS was applied without any drug application (LFS control). After conditioning electric stimulation, JOR blocks were repeated every 5 min for 1 h. LFS consisted of 1200 rectangular pulses (500 μs) applied with a frequency of 1 Hz and stimulus intensities of 1.5 times the I_{JOR}.

Onset and end of each single JOR sweep were manually marked by cursors applying the Signal software. Electromyographic recordings did not show any spontaneous activity of the digastric muscle and reflex activity was always well-defined. Duration and integral of the JOR were calculated in the time window between onset and end of the reflex in each single sweep by the Signal software (Fig. 1). Arithmetic mean and standard error were calculated (mean ± SEM). One and two-way repeated measures analyses of variance (ANOVA) were applied to test statistically significant differences within and between groups (LFS control,

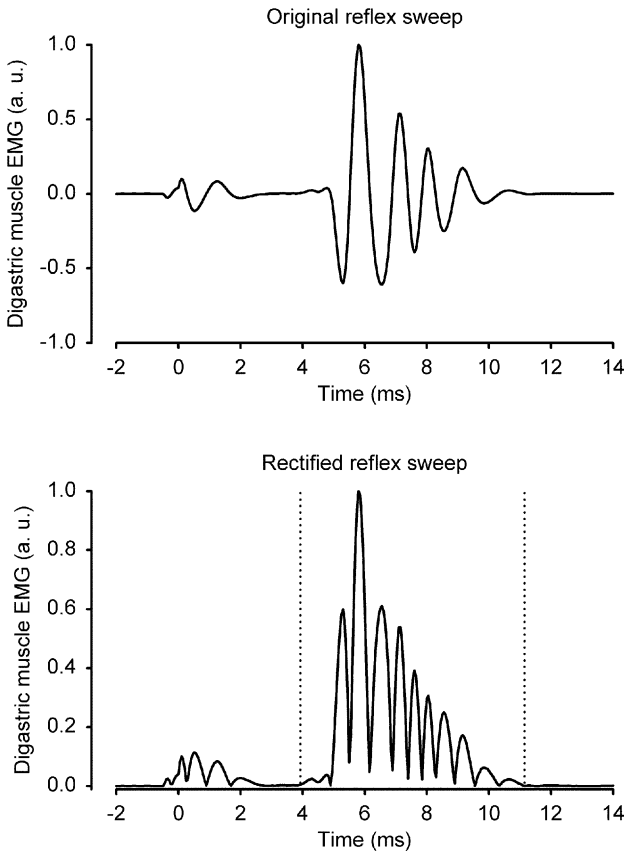

Fig. 1. Analysis of single reflex sweeps. An original single reflex sweep (upper trace) was rectified (lower trace) and onset and end latencies were determined by cursors (dotted lines). The duration corresponds to the time difference between onset and end latencies. The gray area under the curve between the latency cursors corresponds to the reflex integral in the single sweep.