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Effects of intravenous metamizole on ongoing and evoked activity of dura-sensitive thalamic neurons in rats

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ABSTRACT

Migraine and tension-type headache (TTH) are the most common forms of primary headaches. A general key mechanism underlying development of both the diseases is the trigeminal system activation associated with the ascending nociceptive transmission via the trigemino-thalamo-cortical pathway. The ventroposteromedial (VPM) nucleus is a key thalamic structure, receiving afferent inflow from the craniofacial region; it holds the third-order neurons responsible for conveying sensory information from the extra- and intracranial nociceptors to the cortex. The VPM is currently seen as a therapeutic target for various antimigraine medications, which is shown to reduce the VPM neuronal excitability. A non-opioid analgesic metamizole is widely used in some countries for acute treatment of migraine or TTH. However, the precise mechanisms underlying anticephalgic action of metamizole remain unclear. The objective of our study performed in the rat model of trigemino-durovascular nociception was to evaluate the effects of intravenously administered metamizole on ongoing and evoked firing of the dura-sensitive VPM neurons. The experiments were carried out on rats under urethane–chloralose anesthesia. Cumulative administration of metamizole (thrice-repeated intravenous infusion of 150 mg/kg performed 30 min apart) in 56% of cases produced a suppression of both the ongoing activity of the thalamic VPM neurons and their responses to dural electrical stimulation. Although the inhibitory effect was prevailing, a number of VPM neurons were indifferent to the administration of metamizole. These data suggest that one of the main components of neural mechanism underlying anticephalgic action of metamizole is suppression of the thalamo-cortical nociceptive transmission associated with trigemino-vascular activation.

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1. Introduction

Migraine and tension-type headache (TTH) are the most common forms of primary headaches (Headache Classification Committee of the IHS, 2013; Robbins and Lipton, 2010). Although these diseases evidently differ in pathogenesis, a general key mechanism underlying the development of both the conditions is the trigeminal system activation associated with the ascending nociceptive transmission via the trigemino-thalamo-cortical pathway (Bendtsen, 2003; Bernstein and Burstein, 2012; Cathcart et al., 2010; Goadsby et al., 2009). The neurons of the trigeminocervical complex (TCC), which converge vascular, meningeal, cutaneous and myofascial afferents from the head and neck (Bartsch and Goadsby, 2003; Sessle, 2000), are shown to form projections to various subcortical brain structures, thalamus being the most important of them (Edvinsson, 2011; Noseda et al., 2008, 2011).

Findings of various neuroanatomical (Edvinsson, 2011; Guy et al., 2005; Liu et al., 2009; Noseda et al., 2011) and neurophysiological (Burstein et al., 2010; Craig and Dostrovsky, 2001; Davis and Dostrovsky, 1988; Shields and Goadsby, 2005, 2006; Zagami and Lambert, 1990) animal studies indicate that the ventroposteromedial nucleus (VPM) is a key thalamic structure, receiving afferent inflow from the craniofacial region; it holds the third-order relay neurons responsible for conveying sensory information from the extra- and intracranial nociceptors to the cortex. The VPM is currently seen as a therapeutic target for various antimigraine medications. Indeed, it has been shown that spike activity of the VPM neurons was suppressed by topically and/or intravenously administered propranolol (Shields and Goadsby, 2005), naratriptan (Shields and Goadsby, 2006), olcegepant (Summ et al., 2010), topiramate (Andreou and Goadsby,2011) or valproate

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(Andreou et al., 2010; Sokolov et al., 2013). These data suggest that one of the main mechanisms underlying antimigraine action of the mentioned drugs is the inhibition of the trigemino-thalamo-cortical nociceptive transmission.

A pyrazolone derivative metamizole—an available and cheap non-opioid analgesic with a good track record of successful clinical application for over 90 years—is widely used in the countries of Eastern Europe, Latin America and Russia to manage pain syndromes of various localization, and particularly headaches (Bigal, 2002; Bigal et al., 2001; Fendrich, 2000; Ramacciotti et al., 2007). The clinical trials show the high efficacy and safety of this drug taken orally or administrated intravenously to abort migraine attack (Bigal et al., 2002a, 2002b; Tulunay et al., 2004) or TTH (Bigal et al., 2002c).

Although the efficacy of metamizole for the acute treatment of headaches has been clinically proven, the precise mechanisms underlying its anticephalgic action remain unclear; that may be due to the deficiency of relevant research-related findings. Previously it has been demonstrated in rats that intravenous administration of metamizole inhibits neuronal responses in the dorsomedial part of the thalamic ventral nucleus to supramaximal electrical stimulation of the nociceptive sural nerve afferents (Carlsson et al., 1988). Considering these findings in combination with data on the prominent role of VPM in the pathophysiology of headaches, in the present work we studied the effects of intravenously administered metamizole on ongoing and evoked firing of the dura-sensitive VPM neurons in a rat model of trigemino-durovascular nociception.

2. Materials and methods

2.1. Animals

Twenty three adult male Wistar rats (body weight 280–360 g) were used for the study. The animals were housed 2–5 per cage and maintained on a 12-h light/dark schedule with unrestricted access to food and water. All experiments were performed in compliance with the Ethical Guidelines of the International Association for the Study of Pain and European Community Council Directive (86/609/EEC). The study protocol and experimental design were approved by the Institutional Animal Care and Use Committees of the Pavlov Institute of Physiology and the First St. Petersburg Pavlov State Medical University. All efforts were made to reduce the number of animals used and to minimize their suffering.

2.2. Anesthesia and surgical preparation

Rats were anesthetized with urethane (800 mg/kg, i.p.; ICN Biomedicals, Aurora, OH, USA) and α-chloralose (60 mg/kg, i.p.; MP Biomedicals, Solon, OH, USA). Every animal, after being given surgical level of anesthesia, was placed on a thermostatically controlled heating pad. Catheters were placed into the femoral vein for administration of anesthetics and test drugs, and into the femoral artery for continuous monitoring of blood pressure. The trachea was intubated and the head of the animal was fixed in a stereotaxic frame. A midline scalp incision was made and two longitudinal windows were drilled through the left and the right parietal bones to expose respectively the superior sagittal sinus and the parietal cortex above the right VPM (Paxinos and Watson, 1998). Bipolar stimulating electrodes were placed on the dura mater in close proximity to the superior sagittal sinus or visible blood vessels taking care not to make contact with the cortex. The area was covered with mineral oil for insulation as well as to prevent dehydration of the tissue. The dura mater on the right side was incised so that the recording electrodes could be lowered into the VPM. The animal was paralyzed using pipecuronium bromide (i.v., 1.2 mg/kg initially, maintenance 0.6 mg/kg as required; Gedeon Richter, Budapest, Hungary) and artificially ventilated with room air (75–100 cycles/min, 2–3 ml per cycle) using a small animal ventilator. Rectal temperature was maintained between 37 and 38 °C. The depth of anesthesia was assessed by monitoring blood pressure responses to noxious stimulation; supplementary anesthetic was administered when necessary to prevent the gross ($>20\%$ from the baseline level) blood pressure fluctuations.

2.3. Electrical stimulation of the dura mater

Bipolar stimulating electrodes with resistance of 50 KΩ consisted of two varnish-insulated silver wires with beads (0.3 mm in diameter) at the end. The dura mater was stimulated using single rectangular pulses of 300–700 μA (15–35 V) with a duration of 0.3–0.5 ms, delivered by a computer-controlled stimulator. The stimulus intensity was 1.5 times of the response threshold.

2.4. Extracellular recordings

Neuronal activity was recorded by varnish-insulated tungsten microelectrodes (World Precision Instruments, Sarasota, FL, USA) with a tip diameter of 1 μm and a resistance of 1 MΩ. The electrodes were lowered into the right VPM in 4-μm steps using a microdrive unit. The signals from the recording electrode were amplified and passed to the analog input of the IBM-compatible computer A/D converter by means of the multifunctional acquisition card (sampling period 25 μs, hardware filters 100–5000 Hz). For online acquisition, processing and displaying of data, the custom-written software was used. In order to isolate the activity of single units from stimulus artifacts, adjacent cell potentials and noise, three-level amplitude discrimination was used online. Signals of low-level amplitude were rejected as noise. Action potentials with amplitude at middle and high levels were considered as generated by individual neurons and processed separately. Recordings of neuronal activity were analyzed as peristimulus time histograms, such that signals gated through the amplitude discrimination were collected in successive bins of 1 ms. For evoked responses, data were collected from 20 recordings (one per 3 s) over 50 ms after each electrical stimulus. For histograms of ongoing activity pseudo stimulation was used, which consisted in using the same software as for constructing histograms of evoked responses, except that electrical stimulation was not actually applied. The histograms had a sweep length of 500 ms and were created automatically from 50 recordings (one per 1 s). All recorded units apart from responses to the dural electrical stimulation were tested for responses to mechanical stimulation of their dural and facial cutaneous receptive fields by von Frey filaments (North Coast Medical, Morgan Hill, CA, USA). Only neurons demonstrating all three kinds of responses were selected for further testing.

2.5. Experimental protocol

Effects of cumulative (3 steps performed 30 min apart, 150 mg/kg per step) intravenous infusion of metamizole sodium (Analgin, Sopharma Pharmaceuticals, Sofia, Bulgaria) were tested in 16 rats over 90 min. A 150 mg/kg dose was chosen as being the minimum analgesic dose of parenterally administered metamizole in rats (Gaertner et al., 2008). Other seven animals received cumulative infusion of equal volumes of isotonic saline and served as control. In each case, baseline (prior intravenous administration of either metamizole or saline) ongoing and electrically evoked neuronal activities were collected three times 5 min apart ($-10, -5$, 0 min). Then the recordings of neuronal firing with simultaneous creation of peristimulus time histograms were performed in 5, 10, 20, and 30 min after each cumulative step. In all experiments, only one unit

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