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POSTERIOR HYPOTHALAMIC MODULATION OF LIGHT-EVOKED TRIGEMINAL NEURAL ACTIVITY AND LACRIMATION

A. KATAGIRI, K. OKAMOTO,* R. THOMPSON AND D. A. BEREITER

Department of Diagnostic and Biological Sciences, University of Minnesota School of Dentistry, Moos Tower 18-186, 515 Delaware Street SE, Minneapolis, MN 55455, USA

Abstract—Enhanced light sensitivity is a common feature of many neuro-ophthalmic conditions and some chronic headaches. Previously we reported that the bright light-evoked increases in trigeminal brainstem neural activity and lacrimation depended on a neurovascular link within the eye (Okamoto et al., 2012). However, the supraspinal pathways necessary for these light-evoked responses are not well defined. To assess the contribution of the posterior hypothalamic area (PH), a brain region closely associated with control of autonomic outflow, we injected bicuculline methiodide (BMI), a GABAa receptor antagonist, into the PH and determined its effect on the encoding properties of ocular neurons at the ventrolateral trigeminal interpolaris/caudalis transition (Vi/Vc) and caudalis/upper cervical cord junction (Vc/C1) regions and on reflex lacrimation in male rats under isoflurane anesthesia. BMI markedly reduced light-evoked (>80%) responses of Vi/Vc and Vc/C1 neurons at 10 min with partial recovery by 50 min after injection. BMI also reduced (>35%) the convergent cutaneous receptive field area of Vi/Vc and Vc/C1 ocular neurons indicating that both intra-ocular and periorbital cutaneous inputs were affected by changes in PH outflow. Light-evoked lacrimation was reduced by >35% at 10 min after BMI, while resting mean arterial pressure increased promptly and remained elevated (>20 mmHg) throughout the 50-min post-injection period. These results suggested that PH stimulation, acting in part through increased sympathetic activity, significantly inhibited light- and facial skin-evoked activity of ocular neurons at the Vi/Vc and Vc/C1 region. These data provide further support for the hypothesis that autonomic outflow plays a critical role in mediating light-evoked trigeminal brainstem neural activity and reflex lacrimation. **© 2013 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: trigeminal subnucleus caudalis, light sensitivity, lacrimation, posterior hypothalamus, descending control.

INTRODUCTION

Enhanced sensitivity to visible light, often referred to as photophobia or photo-oculodynia (Lebensohn, 1951; Digre and Brennan, 2012), causes a wide range of ocular sensations that can vary in intensity from mild discomfort to intolerable pain. Among the conditions most often associated with photophobia are included: eye injury or inflammation (Custer and Reistad, 2000; Cordero-Coma et al., 2007), blepharospasm (Hallett et al., 2008), retinal dystrophies (Prokofyeva et al., 2011) and some forms of chronic headache (Goadsby et al., 2008; Noseda and Burstein, 2011).

The diversity of conditions associated with photophobia suggests multiple underlying mechanisms; however, a common feature that may link exposure to light with somatic sensation is the activation of trigeminal sensory nerves (Lebensohn, 1951; Digre and Brennan, 2012). Neuroimaging data revealed specific activation patterns in the trigeminal ganglion (TG) and brainstem in a patient with corneal abrasion by visible light stimulation (Moulton et al., 2009). Exposure to bright light in the rat was sufficient to produce a discrete pattern of Fos-positive neurons at the trigeminal interpolaris/caudalis transition (Vi/Vc) and trigeminal subnucleus caudalis and upper cervical spinal cord junction (Vc/C1) regions (Okamoto et al., 2009), the main terminal zones for trigeminal afferent fibers that innervate the eye (Marfurt and del Toro, 1987; Panneton et al., 2010). Recently we provided evidence that light-evoked trigeminal brainstem neural activity depended on neurovascular events within the eye. Exposure to increasing intensities of light was accompanied by progressive increases in choroidal blood flow that preceded the elevation in trigeminal brainstem neural activity, responses that were prevented by intravitreal injections of vasoactive agents (Okamoto et al., 2012). Early clinical studies found that ocular instillation of epinephrine greatly reduced the sensitivity to bright light in patients with persistent ocular inflammation (Lebensohn, 1934), while light-evoked eye spasm (McCann et al., 1999) and photo-oculodynia and reduced tear secretion in idiopathic ocular pain patients were reversed by cervical sympathetic ganglion

*Corresponding author. Tel: +1-612-626-2768; fax: +1-612-626-2651.
E-mail address: okamo007@umn.edu (K. Okamoto).
Abbreviations: BMI, bicuculline methiodide; CH, cluster headache; CO, cornea only; MAP, mean arterial pressure; NS, nociceptive specific; PAG–RVM, periaqueductal gray–rostral ventromedial medulla system; PH, posterior hypothalamus; RF, receptive field; Rmag, response magnitude; SD, standard deviation; SSN, superior salivatory nucleus; TBNC, trigeminal brainstem nuclear complex; TG, trigeminal ganglion; Vc, trigeminal subnucleus caudalis; Vc/C1, trigeminal subnucleus caudalis and upper cervical spinal cord junction; Vi, trigeminal subnucleus interpolaris; Vi/Vc, trigeminal subnucleus interpolaris/caudalis transition; WDR, wide dynamic range.

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blockade (Fine and Digre, 1995). Although these studies suggest sympathetic nervous system involvement in abnormal light sensitivity, little is known about the central pathways that influence sympathetic outflow relevant for light responsiveness in the trigeminal sensory system.

The posterior hypothalamus (PH) has long been associated with sympathetic outflow and pain modulation in humans (Sano et al., 1970, 1975). Short-term PH stimulation in multiple sclerosis patients reduced neuralgic-like pain in the territory of the ophthalmic branch of the trigeminal nerve (Cordella et al., 2009), while long-term stimulation of PH has been used successfully to treat drug-resistant attacks of cluster headache (CH) (Leone et al., 2008). CH is the most common of the trigeminal autonomic cephalalgias and is characterized by strictly unilateral periorbital pain, ipsilateral lacrimation and conjunctival injection (May et al., 1999, 2006; Leone and Bussone, 2009). Nitrate-induced pain in chronic CH patients evoked a unilateral increase in regional cerebral blood flow in the PH (May et al., 1998), while acute PH stimulation in CH patients caused ipsilateral activation in TG and trigeminal spinal nucleus (May et al., 2006). To address the issue of PH stimulation and light-evoked trigeminal brainstem neural activity and reflex lacrimation, we injected the GABAa receptor antagonist, bicuculline methiodide (BMI), into the PH of anesthetized male rats. It is well established that PH outflow is under strong GABAergic inhibitory influence and that GABA disinhibition evokes prompt increases in sympathetic activity (Wible et al., 1988) and defense reaction behavior (Shekhar and DiMicco, 1987).

EXPERIMENTAL PROCEDURES

The animal protocols were approved by the Institutional Animal Care and Use Committee of the University of Minnesota (USA) and conformed to the guidelines set by The National Institutes of Health guide for the care and the use of laboratory animals (PHS Law 99-158, revised 2002). All efforts were made to minimize the number of animals used for experiments and their suffering.

Electrophysiology procedures

Animals. Male rats (270–350 g, Sprague–Dawley, Harlan, Indianapolis, IN, USA) were anesthetized initially with pentobarbital sodium (70 mg/kg, i.p.). Catheters were positioned in the right femoral artery for monitoring blood pressure and jugular vein for drug infusion (gallamine triethiodide, 20 mg/kg/h, at the time of recording). After tracheotomy animals were respired artificially with oxygen-enriched room air and anesthesia was maintained with isoflurane (1.2–2.0%). Expiratory end-tidal CO_2 (3.5–4.5%), mean arterial pressure (MAP, 90–120 mmHg) and body temperature (37 °C) were monitored continuously and kept within normal range. Animals were placed in a stereotaxic frame and a portion of the C1 vertebra was removed to expose the lower brainstem and upper cervical dorsal horn. The exposed brainstem surface was bathed in warm mineral oil. Single neurons were recorded from the ventrolateral Vi/Vc transition or superficial laminae (laminae I–II) at Vc/C1 region. Neurons recorded at the Vi/Vc region were approached at an angle of 28° off vertical and 45° off midline, and 1.5–2.0 mm below the brainstem surface. For neurons in superficial laminae at the Vc/C1 region, the electrode was directed at an angle of 43° off vertical, 60° off midline, and the depth of recording was within 250 μm of the dorsal brainstem surface. Extracellular unit activity was recorded using tungsten microelectrodes (5–9 Mohm; Frederick Haer Inc., Bowdoinham, ME) and amplified, discriminated, stored and analyzed offline using a PowerLab interface and LabChart software (AD Instruments, Colorado Spring, CO, USA).

Characterization of light-responsive ocular neurons. The search stimulus consisted of gently swiping a fine camelhair brush across the ocular surface (e.g., cornea surface and conjunctiva). All units included in this study were activated by mechanical stimulation of both the cornea and conjunctiva. Units with a convergent cutaneous receptive field (RF) were classified as wide dynamic range (WDR) or nociceptive specific (NS) based on the responses to a low force von Frey filament (1.2 g) and pinch with blunt forceps as described previously (Hirata et al., 1999, 2004). Neurons with no apparent cutaneous RF were classified as cornea only (CO). The ocular surface was kept moist with artificial tears throughout neural recording experiments.

Light stimulation and experimental design. One neuron was recorded from each animal preparation and only those neurons responsive to light were included for further analysis. Light stimulation was delivered from a thermal-neutral fiber optic halogen source (150 W; Cole Parmer, Vernon Hills, IL, USA) positioned 5 cm from the left ocular surface under dim ambient light conditions. Light intensity was measured at the ocular surface with a lux meter (Control Co., Friendswood, TX, USA). High-intensity light stimuli (2×10^4 lux, 30 s duration) were presented up to four times in each experiment in a repeated design.

Microinjection of GABAa receptor antagonist into the PH. The GABAa receptor antagonist, BMI (1 mM, pH 7.2; Sigma) dissolved in artificial cerebral spinal fluid (aCSF), or vehicle was injected ipsilateral to the stimulated eye via a glass micropipette positioned 4.0–4.6 mm posterior to bregma, 0.5 mm off midline and 7.3–7.6 mm ventral to the cortical surface 10 min prior to light stimulation. Off-target controls received injections of BMI placed 0.5–0.7 mm dorsal–lateral to PH and ipsilateral to light stimulation. The dose of BMI used was shown previously to inhibit dura-evoked second-order trigeminal brainstem neurons and to elevate arterial blood pressure (Bartsch et al., 2004). Injections of BMI or vehicle were delivered slowly over 60 s in a total volume of 100 nl.

Tear volume

A separate group of male rats (320–400 g, Sprague–Dawley) was anesthetized initially with pentobarbital

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