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Neonatal sensory nerve injury-induced synaptic plasticity in the trigeminal principal sensory nucleus

Fu-Sun Lo *, Reha S. Erzurumlu

Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD 21201, USA

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ABSTRACT

Sensory deprivation studies in neonatal mammals, such as monocular eye closure, whisker trimming, and chemical blockade of the olfactory epithelium have revealed the importance of sensory inputs in brain wiring during distinct critical periods. But very few studies have paid attention to the effects of neonatal peripheral sensory nerve damage on synaptic wiring of the central nervous system (CNS) circuits. Peripheral somatosensory nerves differ from other special sensory afferents in that they are more prone to crush or severance because of their locations in the body. Unlike the visual and auditory afferents, these nerves show regenerative capabilities after damage. Uniquely, damage to a somatosensory peripheral nerve does not only block activity incoming from the sensory receptors but also mediates injury-induced neuro- and glial chemical signals to the brain through the uninjured central axons of the primary sensory neurons. These chemical signals can have both far more and longer lasting effects than sensory blockade alone. Here we review studies which focus on the consequences of neonatal peripheral sensory nerve damage in the principal sensory nucleus of the brainstem trigeminal complex.

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Contents

1. Neonatal sensory nerve damage

Obstetric injuries to the brachial plexus during birth and orofacial injuries and fractures in young children are common occurrences which can lead to permanent brachial plexus palsy or trigeminal nerve pathologies (see reviews by Alcalá-Galiano et al., 2008; Eggensperger Wymann et al., 2008; Sandmire et al., 2008). While these neurological cases are extensively studied at the peripheral nerve level, their CNS

Abbreviations: AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AHP, after hyperpolarization; AP, action potential; BSTC, brainstem trigeminal complex; CO, cytochrome oxidase; EPSP, excitatory postsynaptic potential; GABA, gamma aminobutyric acid; Iba-1, ionized calcium binding adaptor molecule; ION, infraorbital branch of the maxillary division of the trigeminal nerve; IPSP, inhibitory postsynaptic potential; LTD, long-term depression; LTP, long-term potentiation; NMDA, N-methyl-D-aspartate; P, postnatal day; PPD, paired-pulse depression; MII, multiple input index analysis; PPF, paired-pulse facilitation; PPR, paired-pulse ratio; PrV, principal sensory nucleus of the trigeminal nerve; SI, primary somatosensory cortex; TCA, thalamocortical axon; TG, trigeminal ganglion; TrV, central trigeminal tract; VGlut1, vesicular glutamate transporter 1; VPM, ventroposteromedial nucleus of the thalamus.

* Corresponding author at: 20 Penn Street, HSF II, S251, Department of Anatomy and Neurobiology, UMB SOM, Baltimore, MD 21201, USA.
E-mail address: fusunlo@gmail.com (F.-S. Lo).

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consequences remain largely unknown. In pain research, drastic changes in the physiology and adult responsiveness of spinal dorsal horn pain circuits following neonatal peripheral nerve damage or foot incisions have been noted (reviewed in Fitzgerald and Walker, 2009; Baccei, 2011). Increasing numbers of studies are now indicating how peripheral nerve damage or injury in neonates can alter peripheral and spinal nociceptive circuits and neuropathic pain states; these studies are recently reviewed in detail (Fitzgerald and McKelvey, this issue; Baccei et al., this issue).

Defining the molecular and cellular consequences of peripheral nerve damage in the developing CNS is critical for a better understanding of the neural response to injury while it is under construction. The rodent trigeminal system (whisker-to-barrel cortex pathway) is an excellent model for studying cellular and molecular mechanisms which underlie both the patterning of neural connections and their plasticity that follow damage to a purely sensory peripheral nerve.

The first relay station of the system *en route* to the thalamus and the neocortex is the trigeminal principal sensory nucleus (PrV) of the brainstem trigeminal complex (BSTC). The BSTC consists of the PrV, the spinal trigeminal subnuclei (oralis, interpolaris, and caudalis), the motor trigeminal nucleus, and the mesencephalic trigeminal nucleus. The ventral portion of the PrV receives central trigeminal axons of the infraorbital nerve (ION), which innervates the 5 rows of whiskers and perioral sinus hairs in common laboratory rodents.

Sensory nerve (ION) damage during perinatal periods dramatically alters patterning in the PrV and leads to long-lasting synaptic changes. This is an invaluable, model system to investigate CNS consequences of peripheral nerve injuries in neonates, at a time when the brain wiring is in progress. To better understand the effects of neonatal sensory nerve damage on the PrV, analyzing the developmental organization and function in this somatosensory nucleus representing the orofacial peripheral fields is of critical importance.

2. Development and organization of the rodent trigeminal system and the PrV

The infraorbital (IO) branch of the maxillary division of the trigeminal nerve is an exclusively sensory nerve. The IO innervates all of the whiskers on the snout. Central axons of the ION convey whisker-specific information to the trigeminal brainstem. Through interaction of target-derived molecular cues and receptors, the trigeminal ganglion (TG) neurons that contribute to the ION establish a topographic and patterned map of the whisker follicles in the trigeminal brainstem (reviewed in Erzurumlu et al., 2006, 2010). Central branches of the ION afferents develop synaptic terminal clusters, which replicate the patterned organization of the whiskers (Erzurumlu and Jhaveri, 1992; Waite et al., 2000). While whisker-specific patterning in the brainstem emerges by E19-20 in the rat (Chiaia et al., 1992; Waite et al., 2000), it emerges at the time of birth in mice (Ma, 1993). Terminal arbors, at this stage have synaptically active boutons, and the postsynaptic responses in the PrV show a predominant N-methyl-D-aspartate (NMDA) component (Waite et al., 2000).

Postsynaptic target neurons in several nuclei of the BSTC organize with respect to the discrete, whisker-specific patterning of afferent terminals, that, in turn, form the barrelettes (Bates and Killackey, 1985; Belford and Killackey, 1979; Erzurumlu et al., 1980; Ma, 1993; Ma and Woolsey, 1984). The mouse and rat PrV appears as a peanut shaped structure, located laterally in coronal sections through the brainstem. The ventral part of the nucleus, largely derived from rhombomere 3 (Oury et al., 2006), contains the barrelettes with the facial axis represented in an inverted fashion (Fig. 1).

The PrV cells receive other inputs in addition to the ION central axons, such as excitatory and inhibitory inputs from caudal brainstem trigeminal nuclei (Furuta et al., 2008; Martin et al., 2014), serotonergic raphe (Lee et al., 2008; Kirifides et al., 2001) and noradrenalinergic locus coeruleus afferents (Simpson et al., 1997, 1999) and corticotrigeminal inputs from the somatosensory cortex (Malmierca et al., 2014; Sanchez-Jimenez et al., 2009, 2013).

The barrelette neurons of the PrV play a key role in transmitting the whisker-related patterning to the contralateral thalamus and the ventroposteromedial nucleus (VPM). Decades ago, Killackey and Fleming (1985) reported that lesion of the neonatal PrV, but not the spinal trigeminal nucleus, abolishes pattern formation in the VPM and barrel cortex. Genetic manipulation studies have also confirmed this finding in the mouse: thalamic and cortical patterns fail to develop when barrelette patterns are absent in the PrV but not in the spinal trigeminal nucleus (Iwasato et al., 1997).

In the VPM, thalamocortical projection neurons recognize the patterning of incoming PrV trigeminothalamic afferents and form

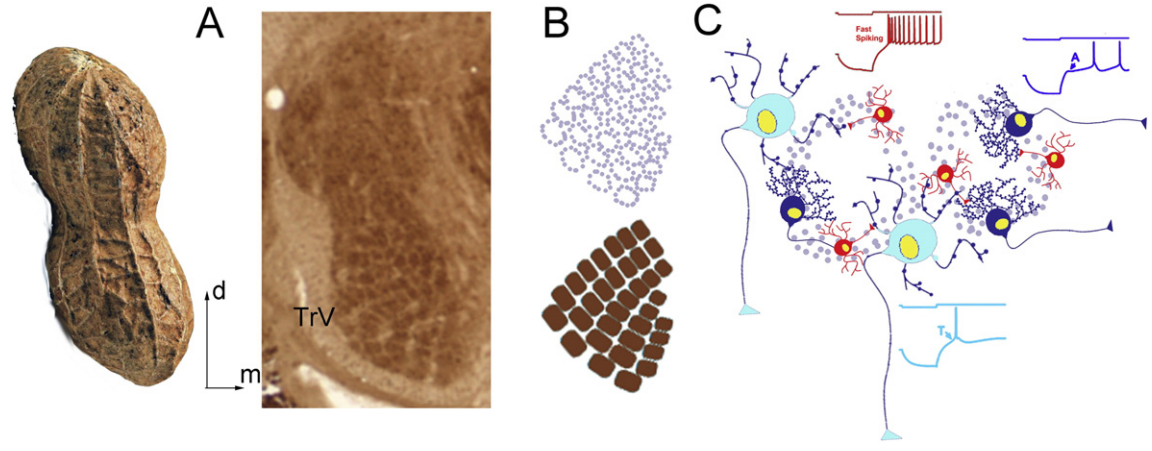

Fig. 1. Barrelettes and the physiological properties of PrV neurons. A. PrV appears as a peanut-shaped structure in coronal sections through the brainstem. The five rows of whiskers on the face are represented in an inverted fashion in the PrV with the dorsal most whiskers represented ventrally and the tip of the nose medially. The nucleus is bordered dorsomedially by the motor trigeminal nucleus and laterally by the central trigeminal tract (TrV); d: dorsal, l; lateral. Cytochrome oxidase histochemistry reveals the barrelettes patterns in the ventral half of the nucleus. B. Schematic representation of the barrelettes as cellular modules (top) and cytochrome oxidase dense patches (bottom). C. Three types of PrV cells in the barrelettes region. The drawings illustrate barrelettes (dark blue) interbarrelette (light blue) and GABAergic interneurons (red). Whole-cell recording in barrelette neuron shows A-type potassium conductance upon membrane depolarization (dark blue record). The same membrane depolarization induces a low threshold spike mediated by T-type calcium channels (light blue record) in interbarrelette neuron. GABAergic neuron gives fast spiking firing to the membrane depolarization (red record).