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STEADY-STATE CENTRIFUGAL INPUT VIA THE LATERAL OLFACTORY TRACT MODULATES SPONTANEOUS ACTIVITY IN THE RAT MAIN OLFACTORY BULB

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Abstract—Mitral and tufted cells in the main olfactory bulb (MOB) of anesthetized rats exhibit vigorous spontaneous activity, action potentials produced in the absence of odor stimuli. The central hypothesis of this paper is that tonic activity of centrifugal input to the MOB modulates the spontaneous activity of MOB neurons. The spontaneous activity of centrifugal fibers causes a baseline of steady-state neurotransmitter release, and odor stimulation produces transient changes in the resulting spontaneous activity. This study evaluated the effect of blocking centrifugal axon conduction in the lateral olfactory tract (LOT) by topically applying 2% lidocaine. Mean spontaneous activity of single bulbar neurons was recorded in each MOB layer before and after lidocaine application. While the spontaneous activity of most MOB neurons reversibly decreased after blockade of the LOT, the spontaneous activity of some neurons in the mitral, tufted and granule cell layers increased. The possible mechanisms producing such changes in spontaneous activity are discussed in terms of the tonic, steady-state release of excitatory and/or inhibitory signals from centrifugal inputs to the MOB. The data show for the first time that tonic centrifugal input to the MOB modulates the spontaneous activity of MOB interneurons and projection neurons. The present study is one of the few that focuses on steady-state spontaneous activity. The modulation of spontaneous activity demonstrated in this study implies a behaviorally relevant, state-dependent regulation of the MOB by the CNS. **© 2017 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: main olfactory bulb, lateral olfactory tract, spontaneous activity, centrifugal input.

INTRODUCTION

The mammalian main olfactory bulb (MOB) receives sensory input from the olfactory epithelium. The MOB is also innervated by numerous centrifugal fibers that originate from neuromodulatory nuclei and cortices (Price and Powell, 1970a,b,c; Davis and Macrides, 1981; Zaborszky et al., 1986; Matsutani and Yamamoto, 2008; Matsutani, 2010). Output neurons from the MOB reciprocally innervate the cortical sources of centrifugal fibers (Nagayama et al., 2010). For example, mitral and tufted cell projections target the piriform cortex, which contains neurons that extend projections back to the MOB, synapsing onto mitral and tufted cells as well as inhibitory networks within the bulb (Ennis et al., 2007; Matsutani and Yamamoto, 2008; Matsutani, 2010; Markopoulos et al., 2012).

Centrifugal fibers also originate from brain nuclei located in the basal forebrain, reticular formation, and pons, which do not receive olfactory signals from the MOB (Zaborszky et al., 1986; McLean and Shipley, 1987; Jiang et al., 1996; Matsutani and Yamamoto, 2008). Neuromodulatory fibers form synapses throughout the MOB (Price and Powell, 1970a,b; Zaborszky et al., 1986; Ennis et al., 2007) and release norepinephrine, serotonin, GABA, and acetylcholine (Zaborszky et al., 1986; Pompeiano et al., 1994; Jiang et al., 1996) into the MOB. The neuromodulatory effects of these neurotransmitters include elevating the excitability of mitral cells (Ciombor et al., 1999), modulating sensitivity, contrast, and synchronization of olfactory signal perception (Devore and Linster, 2012), regulating olfactory learning and olfactory memory (Fletcher and Chen, 2010), and maintaining olfactory circuits (Leo and Brunjes, 2003; Ennis et al., 2007; Ennis and Hayar, 2008; Matsutani and Yamamoto, 2008).

Cortical and neuromodulatory centrifugal fibers reach the MOB via two distinct pathways. The largest, termed the extrinsic centrifugal fiber projection by Laaris et al., 2007, is clearly differentiated from the lateral olfactory tract (LOT), and includes fibers from the anterior olfactory nucleus (AON), anterior commissure, and medial forebrain bundle (Ennis, personal communication). More than half of the centrifugal fibers to the MOB project through the AON (Carson, 1984), and the majority of these centrifugal fibers originate from primary olfactory cortices (Matsutani and Yamamoto, 2008; Matsutani, 2010; Markopoulos et al., 2012). However, the LOT also

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Abbreviations: ACSF, artificial cerebral spinal fluid; AON, anterior olfactory nucleus; EPL, external plexiform layer; GCL, granule cell layer; GL, glomerular layer; HDB, horizontal limb of the diagonal band of Broca; Hz, hertz; LOT, lateral olfactory tract; MCL, mitral cell layer; MOB, main olfactory bulb; ON, olfactory nerve; ONL, olfactory nerve layer.

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contains centrifugal fibers originating from olfactory cortices as well as the horizontal limb of the diagonal band of Broca (HDB) (Price and Powell, 1970b; Pinching and Powell, 1972; Davis and Macrides, 1981; Zaborszky et al., 1986; Niedworok et al., 2012). The HDB contains both cholinergic and GABAergic neurons (Zaborszky et al., 1986; Jeune et al., 1995; Niedworok et al., 2012), and thus, potentially supplies excitatory and inhibitory influences to bulbar neurons.

Most of what is known about the functions of centrifugal input to the MOB comes from electrophysiological and behavioral studies where centrifugal fibers or their sources are stimulated, and from studies that examine the effects of blocking or ablating centrifugal inputs (Inokuchi et al., 1987; Jiang et al., 1996; Kiselycznyk et al., 2006; Ma and Luo, 2012; Markopoulos et al., 2012). These studies demonstrate that centrifugal input shapes bulbar activity in response to stimulation and effects odorant-related behaviors. However, these studies provide less information about the impact of centrifugal input in the absence of stimulation. Reducing centrifugal fiber input in the LOT has been shown to alter local field potentials in the MOB (Gray and Skinner, 1988). Prior studies have demonstrated that certain brain nuclei such as the HDB and the locus coeruleus are active at rest (Jiang et al., 1996; Linster and Hasselmo, 2000). These studies suggest that some centrifugal fibers are active without any imposed stimulation. However, the degree to which tonic centrifugal fiber activity modulates the spontaneous activity of individual MOB neurons remains largely unknown.

The present experiments examine the effects of steady-state centrifugal fiber input on the spontaneous activity of single units in the MOB. Spontaneous activity in sensory networks contributes to the background activity over which sensory signals must be detected, thereby setting the signal-to-noise ratio. Spontaneous activity also increases the dynamic range of sensory circuits so that responses can be represented as increases or decreases in activity (Chaput et al., 1992). The neurochemical environment of the MOB in its resting steady state is likely determined by tonic release of neurotransmitters from spontaneously active MOB neurons and the release of neurotransmitters from active centrifugal fibers. The spontaneous activity of mitral and tufted cells, in turn, contributes to the neurochemical environment of the central olfactory structures to which they project (Brunjes et al., 2005).

While the levels of spontaneous activity in the MOB *in vivo* have been reported to be quite robust, *in vitro* preparations of MOB slices, after denervation of sensory and centrifugal fibers, still exhibit low levels of spontaneous activity. Although centrifugal fiber activity is clearly not the only source of modulatory influences on bulbar neurons, it remains unclear to what extent steady-state centrifugal input contributes to their spontaneous activity. Therefore, the present study identifies tonic centrifugal fiber input to the MOB as a key regulator of spontaneous activity of bulbar neurons *in vivo*.

EXPERIMENTAL PROCEDURES

Ethical approval

Experimental procedures were conducted in agreement with the Institutional Animal Care and Use Committee (IACUC) protocol 10-05-20-01 at the University of Cincinnati. The experimental methods utilized in this study have been described in prior reports (Nica et al., 2010; Stakic et al., 2011) and are only briefly described below. Twenty-nine male Sprague–Dawley rats (Charles River Laboratories; Wilmington, Massachusetts) ranging in weight from 205 to 442 g were used in this study. The animals were housed with a 12-h light/dark cycle with access to food and water *ad libitum*. Anesthesia was provided prior to surgical procedures by an intraperitoneal injection of 4% chloral hydrate at the initial loading dose of 400 mg/kg (10 ml/kg). Animals were additionally implanted with an I.P. catheter so that additional anesthesia could be administered as needed. Although anesthetic drugs can alter spontaneous activity (Jiang et al., 1996; Rinberg et al., 2006), the specific anesthetic protocol was designed to minimize such effects. A surgical plane of anesthesia was maintained throughout the preparation of the animals for recording sessions. Parietal cortex EEGs were closely monitored to ensure appropriate levels of anesthesia. For electrophysiological recordings, the plane of anesthesia was maintained such that a hard toe pinch failed to elicit a reflexive withdrawal response, but desynchronized the EEG. Respiratory rate was also closely monitored as an additional measure of the depth of anesthesia. Lidocaine was applied to surgical wounds to provide local anesthesia. Animals were placed on a heat pad so that animal body temperature could be maintained at 37 ± 0.5 °C.

Surgical preparation

Exposure of the dorsal aspect of the MOB was accomplished by removing part of the frontal bone. The LOT was then exposed by removing the lateral aspect of the temporal bone. In some experiments, olfactory nerve (ON) bundles were exposed by removing the caudal portion of the nasal bone. A reference electrode was inserted into the muscles of the neck. The LOT, MOB, and ON were occasionally wetted with artificial cerebral spinal fluid (ACSF) which contained (in mM): 126 NaCl, 25 $NaHCO_3$, 5.0 glucose, 1.25 NaH_2PO_4-H_2O, 2.5 KCl, 1.0 MgCl, 2.0 $CaCl_2$.

Positioning of stimulation electrodes

To evoke field potentials used to estimate recording electrode depth, determine the efficacy of lidocaine blockade, and assess the integrity of specific pathways following application of lidocaine (detailed below), one bipolar stainless steel electrode was positioned to contact the ventral LOT where the tract is most

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