

OLFACTORY BULB MONOAMINE CONCENTRATIONS VARY WITH TIME OF DAY

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Abstract—The olfactory bulb (OB) has been recently identified as a circadian oscillator capable of operating independently of the master circadian pacemaker, the suprachiasmatic nuclei of the hypothalamus. OB oscillations manifest as rhythms in clock genes, electrical activity, and odor sensitivity. Dopamine, norepinephrine, and serotonin have been shown to modulate olfactory information processing by the OB and may be part of the mechanism that underlies diurnal changes in olfactory sensitivity. Rhythmic release of these neurotransmitters could generate OB rhythms in electrical activity and olfactory sensitivity. We hypothesized that these monoamines were rhythmically released in the OB. To test our hypotheses, we examined monoamine levels in the OB, over the course of a day, by high-performance liquid chromatography coupled to electrochemical detection. We observed that dopamine and its metabolite, 3-4-dihydroxyphenylacetic acid, rhythmically fluctuate over the day. In contrast, norepinephrine is arrhythmic. Serotonin and its metabolite hydroxyindoleacetic acid appear to rhythmically fluctuate. Each of these monoamines has been shown to alter OB circuit behavior and influence odor processing. Rhythmic release of serotonin may be a mechanism by which the suprachiasmatic nuclei communicate, indirectly, with the OB.
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Key words: dopamine, norepinephrine, serotonin, olfaction, diurnal, rhythm.

INTRODUCTION

The olfactory bulb (OB) is one of the few identified circadian oscillators in the brain that is capable of

continued rhythmicity without input from the suprachiasmatic nuclei of the hypothalamus (SCN), called the “master circadian pacemaker.” However, the mechanisms that generate the OB’s oscillations are unknown. The purpose of this study was to determine if the content of dopamine (DA), norepinephrine (NE), or serotonin (5-HT) varied across 24 h and was therefore a possible mechanism underlying OB rhythmicity. Ablation of the SCN affects the period length of OB rhythms (Granados-Fuentes et al., 2004), yet the SCN do not have a known direct connection to the OB. The two structures may interact via OB connection to the lateral hypothalamus (Scott and Pfaffmann, 1967), the SCN connections to the locus coeruleus (LC), the SCN connections to the dorsal hypothalamus that project to the raphe nuclei (RN), or the SCN connections to the intergeniculate leaflet that project to the olfactory tubercle and the lateral olfactory tract (for review, see Morin, 2012). Both the OB and the SCN receive input from the RN and the LC. The RN release 5-HT into the OB and SCN, while the LC releases NE into the OB and SCN; the OB cell types and interactions are depicted in Fig. 1 (McLean and Shipley, 1987, 1991; Gómez et al., 2005). 5-HT and 5-HT agonists affect SCN rhythms (Prosser et al., 1993) and, in the OB, affect learning and memory (for review, see Fletcher and Chen, 2010) and synaptic transmission (Hardy et al., 2005; Petzold et al., 2009). Rhythmic release of 5-HT into the OB would likely affect how well animals perform on memory tasks as well as affecting OB electrical responses to odorants, depending on the time of day. 5-HT and NE may have additive effects (Yuan et al., 2003), but NE has many varied effects in the OB by itself (for review, see Linster et al., 2011). NE alters odor discrimination and habituation (Guerin et al., 2008), affects learning and memory (Fletcher and Chen, 2010), affects cell death and survival (Veyrac et al., 2005), and affects OB synaptic transmission (Trombley and Shepherd, 1992; Jiang et al., 1996; Ciombor et al., 1999; Gire and Schoppa, 2008; Nai et al., 2010). Rhythmic release of NE by the LC into the OB would alter synaptic transmission and OB circuit dynamics, depending on the time of day that NE was released.

Both NE and 5-HT could be released into the OB by SCN activity, and both neurotransmitters have been shown to affect SCN and OB synaptic transmission; we, therefore, hypothesized that these two neurotransmitters affect OB rhythms. However, DA also has multiple effects on neurons within the OB and is released by tyrosine hydroxylase-positive juxtglomerular cells,

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Abbreviations: 5-HT, serotonin; ANOVA, analysis of variance; DA, dopamine; DOPAC, 3-4-dihydroxyphenylacetic acid; HIAA, hydroxyindoleacetic acid; HPLC-EC, high-performance liquid chromatography using electrochemical detection; HVA, homovanillic acid; LC, locus coeruleus; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; OB, olfactory bulb; pg, picograms; RN, raphe nuclei; SCN, suprachiasmatic nuclei of the hypothalamus.

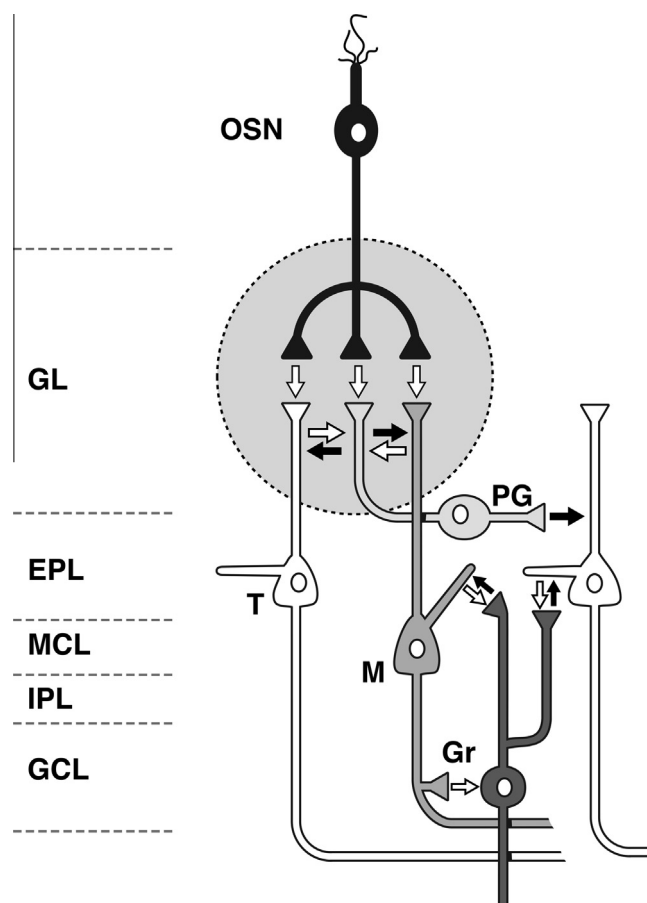


Fig. 1. Circuit diagram of the olfactory bulb and distribution of monoamines. This diagram shows the layers, primary neuronal populations, and synaptic connections of the olfactory bulb (OB). The white arrows represent excitatory connections; the black arrows represent inhibitory connections. Noradrenergic fibers from the locus coeruleus terminate in the inner plexiform layer (IPL) and granule cell layer (GCL), with lower levels of innervation to the external plexiform layer (EPL) and mitral cell layer (MCL). There is very little noradrenergic input to the glomerular layer (GL). Serotonergic fibers from the raphe nucleus project to all layers of the OB: the densest innervation is in the GL, and the MCL, IPL, and GCL are also densely innervated. The EPL is only sparsely innervated by raphe axons. There are no outside dopaminergic projections to the OB. Intrinsic dopaminergic neurons in the OB consist of a subpopulation of neurons within the GL. OSN, olfactory sensory neuron; PG, periglomerular neuron; T, tufted cell; M, mitral cell; Gr, granule cell.

which are among the targets of 5-HT and NE in the OB (for review, see [Cave and Baker, 2009](#)). DA stimulates subventricular zone neurogenesis ([Kim et al., 2010](#)), affects odor discrimination ([Escanilla et al., 2009](#)), and affects synaptic transmission in the OB ([Berkowicz and Trombley, 2000](#); [Ennis et al., 2001](#); [Davila et al., 2003](#)). Rhythmic changes in DA content may alter OB circuit dynamics across the day. Because DA is co-released with gamma-aminobutyric acid (GABA; [Maher and Westbrook, 2008](#)), outside serotonergic input may activate dopaminergic (DAergic) cells, stimulate DA and GABA release, and decrease glomerular responses to odors, in addition to 5-HT's other effects.

We hypothesized that monoamine content in the OB exhibits daily oscillations, distinct from the bulb's faster electrical oscillations. To test this hypothesis, we used high-performance liquid chromatography with electrochemical detection (HPLC-EC) to measure the monoamine content in the OB. We found that the DA concentration fluctuates over 24 h, while NE concentration does not. The concentration of 5-HT

follows a 10–12 h rhythm, with nadir 2 h prior to lights out. These data suggest that OB circuit dynamics, among other behaviors, are altered across the day and cannot be considered static or immune to circadian influences. Additionally, this work supports the idea that the circadian system affects olfactory function ([Granados-Fuentes et al., 2011](#)).

EXPERIMENTAL PROCEDURES

Animals

Male and female Sprague–Dawley rat pups (Charles River, Raleigh, NC, USA), aged postnatal days 21–23, were kept in standard rat cages under a 12-h light, 12-h dark cycle (lights on at 0700 h EST; ZT0). Water and rat chow were available *ad libitum*. Tissues from 5 to 7 individual animals were collected at each time point, for a total of 135 animals used for this study. Animals were anesthetized using isoflurane and killed by decapitation. During the night, tissue collection was performed under

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