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Research paper

The serotonin releaser fenfluramine alters the auditory responses of inferior colliculus neurons

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Abstract

Local direct application of the neuromodulator serotonin strongly influences auditory response properties of neurons in the inferior colliculus (IC), but endogenous stores of serotonin may be released in a distinct spatial or temporal pattern. To explore this issue, the serotonin releaser fenfluramine was iontophoretically applied to extracellularly recorded neurons in the IC of the Mexican free-tailed bat (*Tadarida brasiliensis*). Fenfluramine mimicked the effects of serotonin on spike count and first spike latency in most neurons, and its effects could be blocked by co-application of serotonin receptor antagonists, consistent with fenfluramine-evoked serotonin release. Responses to fenfluramine did not vary during single applications or across multiple applications, suggesting that fenfluramine did not deplete serotonin stores. A predicted gradient in the effects of fenfluramine with serotonin fiber density was not observed, but neurons with fenfluramine-evoked increases in latency occurred at relatively greater recording depths compared to other neurons with similar characteristic frequencies. These findings support the conclusion that there may be spatial differences in the effects of exogenous and endogenous sources of serotonin, but that other factors such as the identities and locations of serotonin receptors are also likely to play a role in determining the dynamics of serotonergic effects.
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Keywords: Fenfluramine; Serotonin; Serotonin receptor; Inferior colliculus; Neuromodulation

1. Introduction

The neuromodulator serotonin is widely dispersed throughout the brain, and alters sensory responses of every modality examined (for example, somatosensory: Waterhouse et al., 1986; Foehring et al., 2002; visual: Waterhouse et al., 1990; Mooney et al., 1996; olfactory: Yuan et al., 2003; auditory: Ebert and Ostwald, 1992; reviewed in Hurley et al., 2004). In the inferior colliculus (IC), a midbrain nucleus that integrates ascending auditory information from multiple brainstem nuclei (reviewed in Irvine, 1992; Oliver and Huerta, 1992; Pollak et al., 2003), serotonin has strong effects on the responses of neurons to auditory stimuli, and can alter such fundamental properties as spike count, frequency tuning, and response latency (Hurley and Pollak, 2001, 2005b). In all previous studies, these changes have been evoked by the application of exogenous serotonin. Knowing more about the dynamics of endogenously released serotonin would contribute to a better understanding of the function of serotonergic modulation in the IC.

Just as for neurotransmitters like GABA and glutamate, serotonin availability in the brain is regulated by the balance between exocytotic release and reuptake by transporters (Blakely and Bauman, 2000). For serotonin, these processes are less confined to synapses than they are for many classical neurotransmitters, and serotonin may travel relatively far from the site of release before encountering a transporter (Bunin and Wightman, 1998). This being the case, the local application of exogenous serotonin could be a reasonable model for the endogenous release of serotonin. On the other hand, levels of endogenously released serotonin could differ regionally or temporally from those

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of exogenously applied serotonin. One reason for this is that serotonergic fibers are denser in some regions of the IC than others, such as the dorsal and external cortices, and also in the dorsomedial region of the central nucleus of the IC in some species including the free-tailed bat (Klepper and Herbert, 1991; Kaiser and Covey, 1997; Hurley and Thompson, 2001). This distribution of fibers may also mean that serotonin clearance is more rapid in regions of high release, since serotonin transporters are located on serotonergic fibers (Nielsen et al., 2006).

Most of the serotonergic fibers found in the IC originate in the dorsal and median raphe nuclei (Klepper and Herbert, 1991). Therefore, the release of endogenous serotonin in the IC could be investigated by activating these nuclei electrically or chemically (for example, Sakai and Crochet, 2001; Pobbe and Zangrossi, 2005; Sheibani and Farazifard, 2006). A disadvantage of this type of manipulation is that it would likely have relatively global effects, since these dorsal raphe neurons innervate extensive regions of the brain, including regions that are known to project to the IC (for example, cochlear nucleus: Zook and Casseday, 1985; Oliver, 1987; Vater and Feng, 1990; Klepper and Herbert, 1991; amygdala: Marsh et al., 2002; Jacobs et al., 1978). Indeed, even single serotonergic neurons may send collaterals to different nuclei along ascending sensory pathways (Kirifides et al., 2001). Thus, stimulating the dorsal raphe nucleus would likely alter the response properties of inputs to the IC as well as those of neurons within the IC itself.

Here, we take another approach to exploring endogenous serotonin release in the IC by locally applying fenfluramine, a serotonin releaser and reuptake inhibitor. Fenfluramine is an amphetamine derivative with selectivity for the serotonergic system that in the short term increases serotonin levels in the brain but over the course of days or weeks may deplete serotonin (Rowland and Carlton, 1986; Schwartz et al., 1989; Baumann et al., 2000; Tao et al., 2002; Rothman et al., 2003; Itzhak and Ali, 2006). This study focuses on the effects of iontophoretically applied fenfluramine on the auditory responses of single IC neurons in a time frame of minutes. Although fenfluramine has often been infused locally into different brain regions (for example, Schwartz et al., 1989; Consolo et al., 1996; Baumann et al., 2000, 2001; Cobb and Abercrombie, 2003; van der Stelt et al., 2005), this study represents the first iontophoretic application of this drug, to our knowledge. In this study, we measure the effects of fenfluramine on the auditory responses of single neurons, assess whether fenfluramine acts by releasing serotonin, and examine the distribution of different effects of fenfluramine relative to recording depth and characteristic frequency.

2. Materials and methods

2.1. Subjects

Experiments were performed on 7 male Mexican free-tailed bats (*Tadarida brasiliensis*) collected under permit from Texas Parks and Wildlife. Prior to surgery, bats were anesthetized by brief exposure to isoflurane fumes followed by intraperitoneal injection of 120 mg/kg ketamine and 5 mg/kg xylazine. When deep anesthesia was achieved as judged by the lack of response to tail and foot pinch, the skin and muscle overlying the skull were incised and deflected. A small hole was drilled above the IC, plainly visible in the contours of the skull. The dura was then incised and the hole covered with a thin layer of surgical-grade silicon gel to prevent drying. Lidocaine gel (2%) was applied topically to surgical surfaces, and the bat was placed in a soft foam holder shaped to its body contours and transported to a sound-attenuated chamber. The head of the bat was immobilized in a custom-made stereotaxic device (Schuller et al., 1986) with a post affixed to the skull by dental cement rostral to the IC. In some cases, a second post was attached caudal to the IC with cyanocrylate gel for additional mechanical stability. The bat was then allowed to waken. Bats usually lie quietly within the recording apparatus. Periodically, topical lidocaine anesthesia was refreshed and the bat was offered water from a dropper. If a bat showed discomfort, as judged by movement that was observed directly or through the recording electrode, a subanesthetic dose of 20 mg/kg ketamine and 1 mg/kg xylazine (1/5 of the surgical dose) was administered. If movement persisted, the experiment was terminated and the bat returned to its home cage. Neurons were recorded during two sessions, with a resting period in the home cage of no less than 10 h between sessions. Before this resting period, bats were reanesthetized with isoflurane, their incisions were sutured, and they were treated with a topical mixture of antibiotic and Lidocaine gels as well as a systemic analgesic (Torbugesic, 1–2 mg/kg). All procedures used in this study were approved by the Bloomington Institutional Animal Care and Use Committee.

2.2. Extracellular recording of single neurons

A total of 95 IC neurons were recorded through single-barreled extracellular pipettes attached in a 'piggy-back' configuration (Havey and Caspary, 1980) to a tribarreled micropipette used for the iontophoresis of drugs. Iontophoresis pipettes were broken to a tip diameter of 10–20 μm, with the single-barreled recording pipette protruding 10–15 μm in front of the multibarreled pipette. The tips of the single-barreled pipettes were filled with 1 M NaCl and had resistances of 8–20 MΩ. Pipettes were connected by a silver-silver chloride wire to a Dagan 2400 amplifier (Minneapolis, MN). Spikes were fed through a spike signal enhancer (FHC model, Bowdoinham, ME) before being digitized through a data acquisition processor board (Microstar, Bellevue, WA). Multibarreled electrodes were positioned above the IC under visual control through a dissecting microscope and lowered with a piezoelectric microdrive (Burleigh/EXFO inchworm,

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