Hearing Research 279 (2011) 74–84

Contents lists available at ScienceDirect

Hearing Research

journal homepage: www.elsevier.com/locate/heares

Context-dependent modulation of auditory processing by serotonin

L.M. Hurley [a,*], I.C. Hall [b]

[a] Indiana University, Jordan Hall/Biology, 1001 E. Third St, Bloomington, IN 47405, USA
[b] Columbia University, 901 Fairchild Center, M.C. 2430, New York, NY 10027, USA

ARTICLE INFO

Article history:
Received 3 October 2010
Received in revised form
13 December 2010
Accepted 20 December 2010
Available online 25 December 2010

ABSTRACT

Context-dependent plasticity in auditory processing is achieved in part by physiological mechanisms that link behavioral state to neural responses to sound. The neuromodulator serotonin has many characteristics suitable for such a role. Serotonergic neurons are extrinsic to the auditory system but send projections to most auditory regions. These projections release serotonin during particular behavioral contexts. Heightened levels of behavioral arousal and specific extrinsic events, including stressful or social events, increase serotonin availability in the auditory system. Although the release of serotonin is likely to be relatively diffuse, highly specific effects of serotonin on auditory neural circuitry are achieved through the localization of serotonergic projections, and through a large array of receptor types that are expressed by specific subsets of auditory neurons. Through this array, serotonin enacts plasticity in auditory processing in multiple ways. Serotonin changes the responses of auditory neurons to input through the alteration of intrinsic and synaptic properties, and alters both short- and long-term forms of plasticity. The infrastructure of the serotonergic system itself is also plastic, responding to age and cochlear trauma. These diverse findings support a view of serotonin as a widespread mechanism for behaviorally relevant plasticity in the regulation of auditory processing. This view also accommodates models of how the same regulatory mechanism can have pathological consequences for auditory processing.

1. Introduction

An important type of auditory plasticity is the influence that behavioral context has on auditory responses at a cellular level. Mechanisms that promote this sort of optimal processing of auditory information during behavioral situations such as social encounters or stressful events are likely to be highly adaptive. The evidence reviewed here supports the monoamine neuromodulator serotonin as a prominent mechanism for linking both internal state and the occurrence of external events with auditory processing. Anatomical studies have long demonstrated widespread projections from serotonergic neurons to the auditory system that are suggestive of pervasive effects of serotonin (Steinbusch, 1981). More recently, there have been an increasing number of studies on the effects of serotonin in the auditory system at multiple levels of analysis, ranging from the modulation of specific ion currents to the involvement of the serotonergic system in auditory perception (Monckton and McCormick, 2002; Robinson, 2007). These studies illustrate that serotonin promotes adaptive 'plasticity' in auditory processing in multiple ways. First, serotonin modifies both intrinsic and synaptic properties of auditory neurons, resulting in a modulation of the responses to input. Second, serotonin influences both short- and long-term plasticity in several auditory regions. Finally, different components of the infrastructure of the serotonergic system within auditory nuclei, including receptor expression, are themselves subject to plasticity, a phenomenon known as 'metamodulation'. Growing evidence that serotonin also strongly influences developmental plasticity in the auditory system is not addressed here (but see Fitzgerald and Sanes, 1999; Luo et al., 2003; Thompson, 2006; Basura et al., 2008; Thompson and Thompson, 2009). In the following review, we first provide a foundation for understanding the role of serotonin in auditory processing by briefly describing the anatomical relationship between the serotonergic and auditory systems, and the influence of different behavioral contexts on serotonin release in the auditory system. We then focus on multiple ways in which serotonin release modulates auditory neural circuitry, and finally assess how these effects of serotonin could influence particular auditory tasks.

Abbreviations: 5-HT, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid; CN, cochlear nucleus; IC, inferior colliculus; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; MSO, medial superior olive; PVCN, posteroventral cochlear nucleus; VNTB, ventral nucleus of the trapezoid body.

* Corresponding author. Tel.: +1 812 856 1991; fax: +1 812 855 6705.
E-mail address: lhurley@indiana.edu (L.M. Hurley).

0378-5955/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.heares.2010.12.015

2. Serotonergic innervation of the auditory system

Summary: Serotonergic projections from raphe nuclei are found broadly throughout the auditory system, with regional specificity in the patterns of innervation and expression of receptors.

The serotonergic system of the brain is a centralized, diffusely projecting network that innervates the auditory system from the level of the cochlea through the cortex (Steinbusch, 1981; Willard et al., 1984; Fitzpatrick et al., 1989; Klepper and Herbert, 1991; Gil-Loyzaga et al., 1997; Kaiser and Covey, 1997; Hurley and Thompson, 2001; Kim et al., 2003; Thompson and Hurley, 2004). The cell bodies of serotonergic neurons are found in a chain of midline raphe nuclei in the brainstem (B1–B9 groups: Jacobs and Azmitia, 1992). The serotonergic fibers found in the auditory system fall into several morphological classes, with the putative release sites for serotonin appearing as swellings or 'varicosities' found at intervals along the fibers (Thompson et al., 1994; DeFelipe et al., 1991). Serotonergic varicosities are not always associated with classical-looking synapses. In conjunction with physiological measurements, the presence of irregular junctional complexes, or the lack of such complexes, suggests that serotonin might have a paracrine-like or extrasynaptic mode of transmission relative to neurotransmitters such as glutamate and GABA (Beaudet and Descarries, 1981; Papadopoulos and Parnavelas, 1991; Bunin and Wightman, 1998). In the auditory cortex, serotonergic contacts in specialized 'basket' clusters of varicosities are lacking or appear irregular, suggesting that extrasynaptic release occurs in at least this auditory region (DeFelipe et al., 1991).

As revealed by immunostaining for serotonin or the serotonin transporter, the serotonergic projections to many auditory nuclei show distinct patterns that are sometimes conserved across vertebrate species. For example, the dorsal cochlear nucleus (CN) and dorsal and external cortices of the inferior colliculus (IC) have somewhat denser networks of serotonergic fibers than do the ventral subdivisions of cochlear nucleus and central IC, in many species (Fig. 1; Klepper and Herbert, 1991; Thompson et al., 1995; Kaiser and Covey, 1997; Hurley and Thompson, 2001; Thompson and Thompson, 2001; Zeng et al., 2007). Similarly, suprageniculate and interlaminar regions of the thalamus possess a greater density of serotonergic fibers than do the principal subnuclei of the medial geniculate body in species such as squirrel monkey and rat (Lavoie and Parent, 1991; Vertes et al., 2010). These conserved patterns have led some authors to speculate that an important role of serotonin in these regions is to modulate the convergence of ascending auditory information with information from descending or non-auditory sources (Klepper and Herbert, 1991; Zeng et al., 2007).

In contrast to these conserved aspects of serotonergic innervation, other brainstem auditory nuclei show substantial species differences in fiber pattern. In particular, the innervation of the lateral and medial superior olives (LSO and MSO) varies among species in both the overall fiber densities and in the tonotopic pattern of fibers. In cat, guinea pig, and bush baby, serotonergic fibers are denser in periolivary regions than in principal nuclei (Thompson et al., 1994; Thompson and Schofield, 2000). In contrast, the LSO and MSO have relatively high fiber densities and uniform fiber distributions in mice, while low-frequency regions of these two nuclei have the highest density of fibers in the Mexican free-tailed bat (Hurley and Thompson, 2001; Thompson and Hurley, 2004). In addition, layer-specific patterns of serotonergic fiber density in auditory cortex are more pronounced in some species such as cat than in others such as cynomolgus monkey (Lewis et al., 1986; Campbell et al., 1987; DeFelipe et al., 1991). This variation suggests that the influence of serotonin might be similar among species in some auditory regions, and not in others.

Clear distinctions in the raphe sources of serotonergic fibers among different auditory regions have not been reported. Both anterograde and retrograde tract tracing studies between the cochlear nucleus or IC and serotonergic nuclei find that the major source of serotonin to both regions is the dorsal raphe nucleus (cell group B6 and B7), with minor contributions from the median raphe (B5 and B8) and even less from more inferior raphe nuclei (Jacobs and Azmitia, 1992). Fibers originating in the dorsal raphe nucleus have even been detected in the LSO, and dorsal raphe neurons label retrogradely after tracer injection into the cochlea (Thompson and Thompson, 2001; Kim et al., 2003). Thus, the innervation of the auditory brainstem and midbrain by different serotonergic neuron groups is relatively uniform, at least at a gross level. At a finer level in auditory cortex, several authors have described layer-specific patterns of morphologically distinct fiber types that have been associated with the dorsal versus median raphe nucleus (Campbell et al., 1987; Kosofsky and Molliver, 1987; DeFelipe et al., 1991; Vu and Törk, 1992). This finding opens the possibility for differential regulation of auditory subregions by projections from different raphe nuclei.

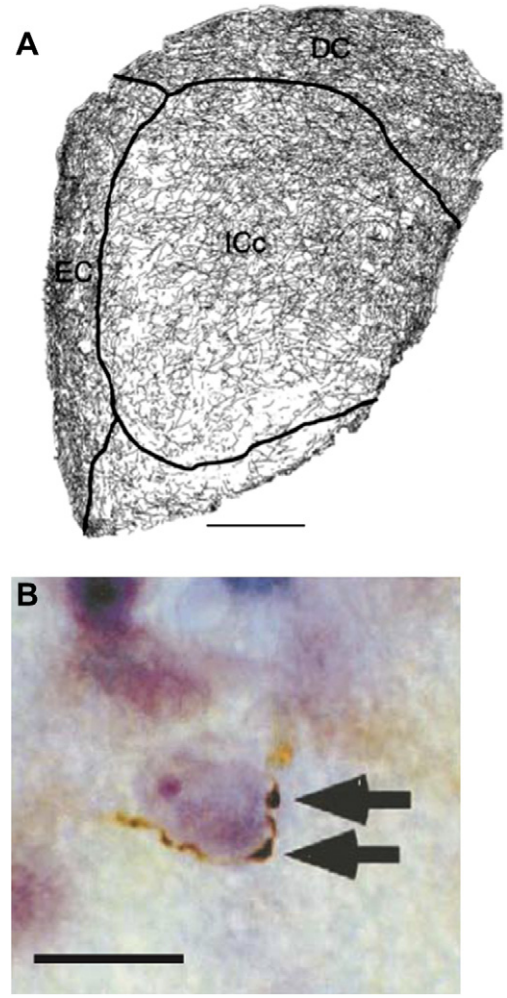

Fig. 1. Immunostained serotonergic projections from the Mexican free-tailed bat (*Tadarida brasiliensis*) showing conserved features of the serotonergic system. A) Camera lucida drawing of serotonergic fibers from the IC. Fibers are densest in the dorsal and external cortices (DC and EC), but are also present in the central nucleus of the IC (ICc). Scale bar = 400 μm. B) Serotonergic varicosities in close apposition to a cresyl-stained cell body in the IC. Scale bar = 10 μm. Figures are reproduced with the permission of Wiley and Sons.

Once released by the raphe projections, serotonin likely activates many different types of serotonin receptors. The serotonergic system is one of the most receptor-diverse neuromodulatory systems. There are 7 molecularly characterized families of serotonin receptor, and

some of these contain multiple receptor types, such as the 5-HT1A and 5-HT1B receptors of the 5-HT1 family (Barnes and Sharp, 1999; Hannon and Hoyer, 2008). Many of these receptor types are present in the auditory system. Members of at least 5 of the 7 families of 5-HT receptors, or the physiological effects of these receptors, have been reported in the IC alone (Chalmers and Watson, 1991; Pompeiano et al., 1992, 1994; Waeber et al., 1994; To et al., 1995; Wright et al., 1995; Bohorquez and Hurley, 2009; Miko and Sanes, 2009). Similar to the serotonergic fibers themselves, there is anatomical evidence for regional distribution of some types of serotonin receptors, most notably the 5-HT1A receptor. Radioligand binding studies indicate that this receptor is more heavily expressed in the IC than in the CN (Thompson et al., 1994). Within both of these nuclei, autoradiographic, immunohistochemical, and riboprobe studies show that this receptor type is restricted to particular nuclear subregions, and expressed in a subset of neurons (Thompson et al., 1994; Thompson and Wiechmann, 2002; Peruzzi and Dut, 2004). The almost bewildering diversity of 5-HT receptors often prompts the question: 'Why are there so many different types?' (Peroutka, 1995). An ultimate answer may lie in the lengthy evolutionary history of serotonin and its companion receptors (Peroutka, 1994, 1995). Functionally, different receptor types influence auditory activity in different ways, as described in a later section.

3. Intrinsic and extrinsic influences on auditory serotonin

Summary: In the auditory system, serotonin increases with behavioral arousal, and fluctuates in response to sensory stimuli, stressful events, and social encounters.

The availability of serotonin in the auditory system is determined by the activity patterns of raphe neurons projecting to auditory regions and by multiple additional mechanisms influencing the release or reuptake of serotonin (Celada and Artigas, 1993; Jacobs and Fornal, 1999; Dahlin et al., 2007; Gasser et al., 2009). Dorsal raphe neurons fire tonically at higher rates in awake animals and at lower rates during sleep, particularly during slow-wave sleep (Jacobs and Fornal, 1999; Portas et al., 2000; Adell et al., 2002; Trulson, 1985; Heym et al., 1982). Superimposed on the tonic spike trains of some raphe neurons are transient changes in firing in response to the presentation of sensory stimuli with short latencies of tens of milliseconds or less, suggesting relatively direct sensory input (Le Moal and Olds, 1979; Mendlin et al., 1996; Heym et al., 1982; Waterhouse et al., 2004; Pum et al., 2008). Further, dorsal raphe firing or serotonin release in some brain regions can correspond to behavioral conditions such as stressful situations, social interaction, or even the value of rewards (Boutelle et al., 1990; Vahabzadeh and Fillenz, 1994; Mas et al., 1995; Clement et al., 1998; Grahn et al., 1999; Hayley et al., 2001; Abrams et al., 2004; Mitsushima et al., 2006; Smith et al., 2006; Kranz et al., 2010).

This range of responses is supported by a broad set of inputs to the dorsal and median raphe nuclei. Regions including hypothalamus, medial and lateral preoptic areas, habenula, amygdala, medial prefrontal cortex, and other cortical areas all project to the dorsal raphe nucleus, sometimes to specific subnuclei (Peyron et al., 1998; Lee et al., 2003). The dorsal raphe nucleus also receives input from more peripheral sensory regions including the retina and vestibular nuclei (Kawano et al., 1996; Cuccurazzu and Halberstadt, 2008). Of direct interest for auditory responses in the dorsal raphe nucleus, neurons retrogradely labeled by the injection of tracer in the dorsal raphe are observed in the cochlear nucleus and a nearby region called the juxta-acoustico-floccular fascicle, proposed to be a multisensory area (Ye and Kim, 2001). These sets of afferents and patterns of activity suggest a role for raphe neurons as integrators of a broad range of direct and indirect sensory and behavioral information, which is then projected onto the activity patterns of auditory neurons.

Fluctuations in serotonin in the CN, IC, and auditory cortex reflect some of the features observed in raphe unit activity, but there are also highly specific patterns of serotonin availability in the auditory system that are important to interpret within an auditory context. Serotonergic activity has been measured in the auditory system with high-performance liquid chromatography performed on microdialytic samples or dissected tissue, or with implanted electrochemical probes that measure the oxidation of serotonin (Cransac et al., 1995; Stark and Scheich, 1997; Liu et al., 2003; Müller et al., 2007; Hall et al., 2010). Consistent with patterns of activity in some raphe neurons, serotonin in the IC corresponds to the general level of behavioral arousal. In mice recovering from anesthesia, serotonin steadily builds relative to a control group of anesthetized mice, plateauing shortly after animals wake (Hall et al., 2010). In awake mice, sensory stimuli can evoke shorter-term changes in serotonin. Several studies using different techniques to measure serotonin have demonstrated that exposure to white noise can alter the levels of serotonin or its main metabolite, 5-hydroxyindoleacetic acid (5-HIAA). Increases in response to white noise have been reported in CN, IC, and primary auditory cortex (Cransac et al., 1998; Hall et al., 2010), while a decrease has been reported in temporal cortex (Müller et al., 2007). Methodological differences in stimulus administration or measurement technique could account for disparities among studies. Even within a single study, however, the tissue content of serotonin in response to a 45-min presentation of white noise varies among CN, IC, and cortex (Cransac et al., 1998). The serotonin content of the dorsal and posteroventral regions of the CN increases with the intensity of white noise varying from 70 to 110 dB SPL after a 45-min presentation. In contrast, no change occurs at any intensity in the IC, and an increase in the 5-HIAA:5-HT ratio occurs only at 70 dB in the primary auditory cortex.

In addition to regional specificity, a second interesting facet of the serotonergic response to sensory stimuli is that it can be highly selective. The serotonergic system responds to a broad range of stimuli of multiple modalities including white noise, light, food, or the odor of predators (Rueter and Jacobs, 1996; Heym et al., 1982; Waterhouse et al., 2004; Smith et al., 2006; Takase and Nogueira, 2008). Out of this limited set of simple stimuli, however, serotonin in the IC of mice changes only in response to noise, increasing significantly within minutes of stimulus onset (Hall et al., 2010). This is true even though several of the other stimuli such as food and odor of predators evoke behavioral responses from mice (investigation/consumption and avoidance, respectively). It may not seem remarkable that out of this set of stimuli, only the auditory stimulus evokes a change in serotonin in an auditory nucleus. Nevertheless, when one considers that the raphe nuclei are not auditory regions per se, this selectivity for stimulus type becomes more striking. The mechanisms underlying the selectivity of the serotonergic response in the auditory system have not been explored, but could include regional differences in the density of raphe projections or the population of reuptake transporters (Klepper and Herbert, 1991; Dahlin et al., 2007; Gasser et al., 2009).

Though underexplored, it is important to note that serotonin in the IC changes in response to stimuli other than broadband noise. In the IC and auditory cortex, extracellular serotonin increases to varying degrees during exposure to stress and social interactions (Stark and Scheich, 1997; Hall et al., 2010, 2011). During restricted movement, a stressful manipulation which limits mobility, extracellular serotonin in the IC increases relative to pre-restriction baseline and remains elevated until the end of the manipulation (Hall et al., 2010). Serotonin rises in auditory cortex during associative training sessions that use footshock, even when conditioned and unconditioned stimuli are unpaired (Stark and Scheich, 1997). Social interaction also triggers a buildup of serotonin with several noteworthy characteristics. Extracellular serotonin levels rise in the

IC of male mice presented with an intruder in their home cages, but only when direct physical interaction between the males is allowed (Hall et al., 2011). Although this increase in serotonin is significant on average, there is substantial variation among individual males. The variation is consistent, in that individual males will show highly correlated responses to different intruders on separate occasions. Finally, the size of the serotonergic response in individual males is correlated with several behaviors, including an indicator of overall activity level (immobility) and a measurement of social assessment (anogenital investigation). These findings suggest that fluctuations in serotonin in the IC may not indicate simply the occurrence of a particular behavioral event, but also the overall behavioral response to that event.

All of these studies provide evidence that the nature of serotonergic signals in the auditory system are more complex than predicted based on the activity patterns of dorsal raphe neurons. Fluctuations in serotonin are responsive to both internal state and to external stimuli. Serotonin levels are relatively high during stressful and social situations. They also change selectively in response to particular stimuli or behavioral contexts, and vary regionally within the auditory system. An additional feature of serotonergic signals in the auditory system that arises from a comparison among studies is that the amplitude and timecourse of changes in serotonin vary according to behavioral circumstance (Fig. 2). During the process of waking from anesthesia, there is a gradual increase (gray line) that plateaus soon after waking (gray arrow). In response to more discrete behavioral contexts, however, serotonin can change more rapidly. During the limited movement stressor described above (black bar), serotonin peaks sharply and declines afterward (dashed line). In contrast, serotonin rises to a peak over the timecourse of a 15-min direct social interaction between males (black bar, sold line). Thus, the availability of serotonin can be compared to a rheostat rather than a binary switch, and the modulatory effects of serotonin may complement the intensities and timecourses of different behavioral situations.

4. Physiological effects of serotonin

Summary: The effects of serotonin at the cellular level are diverse, and encompass pre-and postsynaptic changes in response properties, as well as alterations in plasticity.

The effects of serotonin on the response properties of auditory neurons have been measured in six different auditory regions: the

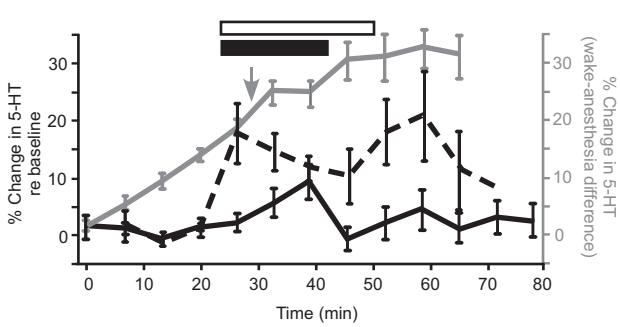

Fig. 2. The timecourse of serotonergic response varies in different behavioral contexts. Extracellular serotonin was measured in the IC of mice with carbon fiber voltammetry. The gray line represents the gradual percent change in serotonin during recovery from anesthesia relative to a control group in which anesthesia was maintained (right *x*-axis: $n = 23$ recovery, $n = 6$ maintained anesthesia). Arrow marks the average time of waking. The dashed line represents the rapid increase in serotonin during placement of mice in a limited movement arena (open bar, $n = 9$). The solid black line represents the increase in serotonin that develops in a resident male mouse during direct interaction with a male intruder (black bar, $n = 22$). Values for the limited movement and social manipulations are normalized to pre-manipulation measurements in the same mice (left *x*-axis).

CN, nuclei of the superior olivary complex including LSO and MNTB, periolivary regions including the ventral nucleus of the trapezoid body (VNTB) and rostral periolivary regions, IC, medial geniculate body, and auditory cortex (for example, Ebert and Ostwald, 1992; Wang and Robertson, 1997; Fitzgerald and Sanes, 1999; Hurley and Pollak, 1999; Ji and Suga, 2007). Within these regions, serotonin is reported to have a wide range of effects on auditory processing, something that is partly due to the variety of physiological paradigms addressed within these studies. Different authors have investigated the influence of serotonin on responses to auditory stimuli *in vivo*, on intrinsic or synaptic characteristic *in vitro*, and on different types of plasticity. Two additional factors contribute to the range of reported effects of serotonin. These are: 1) the array of serotonin receptor types that influence neural responses in the auditory system and 2) the selective targeting of specific cell types, either by the arrangement of serotonergic terminals or by cell-specific receptor expression.

The effects of only 3 of the 7 serotonin receptor families, 5-HT1, 5-HT2, and 5-HT3 receptors, have been directly studied electrophysiologically in the auditory system (Fitzgerald and Sanes, 1999; Hurley, 2006; Mizutani et al., 2006; Ji and Suga, 2007; Bohorquez and Hurley, 2009; Miko and Sanes, 2009). Functionally, these different serotonin receptor types have distinct and consistent effectors and subcellular localizations. The 5-HT1 and 5-HT2 families are metabotropic, as are four of the five additional serotonin receptor families (Barnes and Sharp, 1999; Hoyer et al., 2002; Hannon and Hoyer, 2008). The 5-HT3 family of cation channels is the exception (Hannon and Hoyer, 2008). Thus, the timecourse of most of the serotonin receptor families is expected to be slower than for classical neurotransmission, complementing the timecourse of fluctuations in serotonin levels during behavior. Each individual 5-HT receptor type has a characteristic set of effects and subcellular distribution. For example, 5-HT1A receptors are localized somatodendritically and open potassium channels, leading to decreased responsiveness to input (Vergé and Calas, 2000; Monckton and McCormick, 2002). 5-HT1B receptors are found on presynaptic axons and terminals, and decrease the release of serotonin as autoreceptors on serotonergic neurons, or of other neurotransmitters as heteroreceptors (Sari, 2004). As expected from their different mechanisms, different serotonin receptor types have distinct effects on auditory neurons, as described below.

There is also strong evidence that specific cell types are targeted by the serotonergic system, either by the structure of serotonergic terminals or by selective expression of receptor types. In primary auditory cortex, basket-type serotonergic terminals surround GABAergic neurons in almost all cases (DeFelipe et al., 1991). Clusters of terminals surrounding GABAergic neurons in the IC (Peruzzi and Dut, 2004) and multipolar cells in the PVCN (Thompson et al., 1994) have also been noted. In the CN, only some neurons express high levels of the mRNA for the 5-HT1A receptor (Thompson and Wiechmann, 2002). In the IC, the majority of GABA-expressing neurons also express 5-HT1A receptors and 5-HT1B receptors (Peruzzi and Dut, 2004), although non-GABA positive neurons express these receptor types too. Demonstrating not only cellular but subcellular specificity, 5-HT2A receptors occur on the cell bodies and apical dendrites of pyramidal neurons in layer II/III of auditory cortex (Basura et al., 2008). Neuronal types that have been functionally characterized *in vivo* may also selectively respond to serotonin or activation of serotonin receptors. For example, in the cochlear nucleus, units with primary-like responses are more frequently affected by serotonin than are neurons with chopper firing patterns (Ebert and Ostwald, 1992). In the IC, 3 separate studies have found that neurons with short first-spike latencies of under 10 ms are less sensitive to serotonin or to the activation of specific 5-HT receptors (Hurley and Pollak, 2005b; Hurley, 2007; Bohorquez and Hurley,

2009). Thus, the two factors of receptor type and cell-specific receptor expression together translate a potentially diffuse release of serotonin into highly specific reconfigurations of auditory circuitry.

The exceptional diversity of receptor types presents the simultaneous problems of distinguishing among the effects of different types of receptors, and integrating these effects into a unified hypothesis of serotonergic function. In the remainder of this section, we describe several functional categories of serotonergic effect and how specific 5-HT receptors relate to these, and the involvement of serotonin in short- and long-term plasticity. We finally discuss how these findings underlie hypotheses on serotonergic function.

4.1. Effects of serotonin and 5-HT receptors on single neurons

The effects of serotonin and its receptors on evoked responses of auditory neurons can be categorized broadly as either suppression or facilitatation. Pharmacological and physiological dissection indicates that even within one of these broad categories, serotonin can act through multiple receptor types, and via pre- or postsynaptic mechanisms. The most commonly reported effect of applying serotonin to auditory neurons is the suppression of responses evoked by simple tones or the stimulation of input fibers, and the suppression of spontaneous activity. This occurs in cochlear nucleus (Ebert and Ostwald, 1992), LSO (Fitzgerald and Sanes, 1999), periolivary regions (Wang and Robertson, 1997), IC (Faingold et al., 1991; Hurley and Pollak, 1999), medial geniculate nucleus of some species (Monckton and McCormick, 2002) and auditory cortex (Ji and Suga, 2007). Suppression can occur via either presynaptic or postsynaptic mechanisms. A candidate for mediating postsynaptic suppression in many cases is the somatodendritic 5-HT1A receptor. This is a widespread receptor type found in multiple auditory nuclei (Thompson et al., 1994; Thompson and Wiechmann, 2002; Peruzzi and Dut, 2004) that typically decreases excitability by opening potassium channels (Vergé and Calas, 2000; Monckton and McCormick, 2002). In the gerbil LSO and the IC of mouse and Mexican free-tailed bat, agonists that activate this receptor type depress responsiveness to the electrical stimulation of input fibers or to auditory stimuli (Fitzgerald and Sanes, 1999; Hurley, 2006, 2007). There is also evidence for a postsynaptic site of serotonin-evoked suppression in the cortical slice preparation; application of serotonin decreases the spiking response and adaptation to injected current, and lowers the input resistance (Rao et al., 2010). Other mechanisms for suppression may be presynaptic. In the rat MNTB slice, inhibition of postsynaptic EPSCs by serotonin is due to a 5-HT1B-evoked reduction in voltage-gated calcium current presynaptically (Mizutani et al., 2006). In rat IC slice, application of serotonin increases the frequency and amplitude of spontaneous inhibitory postsynaptic currents (IPSCs), likely by a 5-HT2-dependent mechanism (Wang et al., 2008). A similar but developmentally transient increase in IPSCs triggered by 5-HT2 activation has been reported in gerbil LSO (Fitzgerald and Sanes, 1999).

Although suppression by serotonin is common, serotonin also facilitates evoked responses in many auditory nuclei (Ebert and Ostwald, 1992; Hurley and Pollak, 1999; Hurley, 2006). In periolivary regions the facilitatory effects of serotonin are dominant (Wang and Robertson, 1997). Similar to suppression, different receptor types may mediate facilitation of spikes either pre- or postsynaptically. 5-HT2 receptors are reported to facilitate tone-evoked responses *in vivo* in several auditory regions. Selective activation of the 5-HT2C receptor, a receptor type that is typically localized postsynaptically, facilitates evoked responses in the IC of Mexican free-tailed bat (Hurley, 2006; Liu et al., 2007), and a broad 5-HT2 agonist facilitates tone-evoked responses in cortex of big brown bat (Ji and Suga, 2007). Some receptors, such as the 5-HT3 receptor, can either increase or decrease responses evoked by auditory stimuli, a phenomenon that is dependent on the level of activity in some neurons (Bohorquez and Hurley, 2009). In two cases, the mechanisms of serotonergic facilitation have been more thoroughly investigated. In the mouse IC, activation of the 5-HT1B receptor strongly facilitates sound-evoked responses and reduces the suppression evoked by tones at 'inhibitory' frequencies (Hurley et al., 2008). Blockade of $GABA_A$ receptors reduces or abolishes 5-HT1B-evoked facilitation. These findings, combined with the localization of the 5-HT1B receptor near presynaptic terminals, support the hypothesis that this receptor reduces the release of GABA presynaptically in the IC. In the medial geniculate nucleus of cat and guinea pig, application of serotonin *in vitro* results in a small membrane depolarization. This depolarization is attributed to an increase in the amplitude and a decrease in the time constant of a hyperpolarization-activated current, I_h (Pape and McCormick, 1989; McCormick and Pape, 1990). By comparison with similar results in the lateral geniculate nucleus, this increase is likely due to a positive shift in the activation curve for this current, and is triggered by a receptor type other than a 5-HT1A or 5-HT2 receptor. This depolarizing effect of serotonin seems to be species-specific, however, since a small hyperpolarization rather than a depolarization is observed in a similar preparation of ferret medial geniculate nucleus (Monckton and McCormick, 2002). Thus, the range of serotonin receptors found in auditory nuclei mediates a comparably wide range of changes in presynaptic and postsynaptic function.

Serotonin-evoked changes in spike timing have not been examined with the same attention as changes in spike rate, but are also a prominent feature of the effects of serotonin (Fig. 3). Serotonin and its receptors significantly alter multiple aspects of the spike timing of single neurons, including first-spike latencies, variability in spike timing (jitter), and interspike intervals (Hurley and Pollak, 2005b; Hurley, 2007; Baldan Ramsey et al., 2010). These are often correlated with serotonin-evoked changes in spike rate, so that decreases in spike rate occur in conjunction with increases in latency and increases in spike rate occur in conjunction with decreases in latency. The 5-HT1A receptor, for example, often increases first-spike latency in addition to suppressing evoked responses. This receptor also often depresses secondary spikes more profoundly than initial spikes, changing the temporal structure of spike trains (Hurley, 2007). Conversely, the 5-HT1B receptor often decreases latency in addition to facilitating evoked spikes, and can unmask secondary spikes within a spike train. Serotonin-evoked changes in spike rate and latency do not always occur together, however, suggesting that they are in some cases controlled by divergent serotonergic mechanisms (Hurley and Pollak, 2005a). In the gerbil LSO *in vivo*, serotonin can also differentially affect onset spikes and subsequent spikes (Hurley et al., 2003). These changes in the temporal structure of auditory responses are an important feature of serotonergic effects that are likely to have a strong influence on auditory encoding.

As striking as they may be, considering the effects of single receptor types in isolation may not provide a complete view of how these same receptors act together, as they presumably would during the release of serotonin. In other sensory regions of the brain, different receptor types cooperatively enact the effects of serotonin (Xiang and Prince, 2003), and the same appears to be true in the auditory system. Different receptor types are suspected to mediate suppression versus facilitation in the same cells in the rat CN (Ebert and Ostwald, 1992), and the effects of the 5-HT2A receptor on some neurons in auditory cortex may be masked by other receptor types (Ji and Suga, 2007). In the mouse IC, two receptors in the 5-HT1 family show an interesting division of effects on different response properties (Baldan Ramsey et al., 2010). When activated by selective agonists in isolation, these receptors have apparently opposite effects as described above. Activation of the 5-HT1A receptor

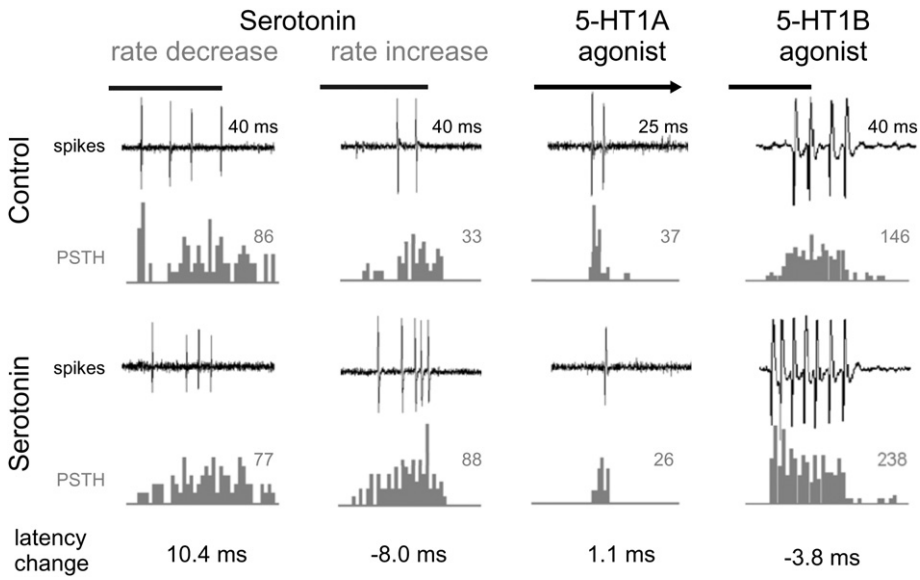

Fig. 3. Examples of the effects of serotonergic agonists on spike rate and spike timing in 4 IC neurons. Each column represents the response of a different neuron in the control and during the iontophoresis of serotonin. Voltage traces of responses to single stimulus presentations (black) are shown above peristimulus time histograms (PSTHs) of responses to 20–32 tone presentations. Black bars represent the presentation of a tone at the characteristic frequency for each neuron (arrowed bar represents a stimulus that continued for an additional 25 ms). Spike counts are denoted by the numbers near PSTHs. Latency changes are the difference in median latency of the initial spikes between drug conditions. Serotonin can increase or decrease latencies in different neurons, while selective agonists of serotonin receptors tend to more uniformly increase (5-HT1A) or decrease (5-HT1B) latencies. Mean first-spike latency changes are significant for all neurons except for the 'serotonin rate increase' neuron at the $p < .001$ level (unpaired *t*-tests, $p = .34$ for the 'serotonin rate increase' neuron). All neurons were recorded *in vivo* in mouse IC.

suppresses responses to tones and often increases spike latencies. In contrast, the 5-HT1B receptor not only facilitates tone-evoked spiking but can reduce spike latencies. Agonists of the two receptor types often influence the responses of the same neuron, indicating that they act on the same neural circuits, presumably both postsynaptically (5-HT1A) and presynpatically (5-HT1B). When these two receptors are activated together, they have an additive effect on spike rate, but changes in the first-spike latency and interspike interval are dominated by the effects of the 5-HT1A receptor. This demonstrates that different 5-HT receptors can interact in nonlinear ways to produce changes in the physiology of auditory neurons. Another potential source of variation in the effects of serotonin is due to interaction with other neurotransmitter systems. For instance, the application of serotonin and norepinephrine has synergistic effects on the evoked responses of IC neurons (Hurley et al., 2004). Although such interactions are likely important to the function of neuromodulatory systems, few studies have directly addressed this issue, so there is not a clear understanding of how prevalent they are *in vivo*.

4.2. Serotonergic effects on plasticity

In many regions of the brain, serotonin plays an important role in different forms of plasticity (Edagawa et al., 2001; Gu, 2002). This also appears to be true in the auditory system, even though only a few studies have directly addressed this issue. Two coincident studies of the 5-HT3 receptor in the IC, one *in vitro* and one *in vivo*, suggest that this receptor influences short-term plasticity. In the gerbil IC slice preparation, an intense stimulation of input fibers transiently increases the number of spikes evoked by a threshold-level current injection, a phenomenon that appears to be postsynaptic (Miko and Sanes, 2009). The 5-HT3 receptor reduces or blocks this transient increase in response. The calcium channel blocker verapamil does the same (Miko and Sanes, 2009). This raises the possibility that the 5-HT3 receptor acts in a parallel or convergent manner with calcium entry, matching well with the fact that this receptor type admits calcium (Hannon and Hoyer, 2008). Interestingly, in the mouse *in vivo* preparation, the 5-HT3 receptor decreases the adaptation of some neurons to different stimulus repetition rates in an activity-dependent manner (Bohorquez and Hurley, 2009). The 5-HT3 receptor does this by facilitating responses more when spike rates are low (at higher repetition rates), and depressing responses more when spike rates are high (at lower repetition rates). Thus, there is an element of activity-dependence to the effects of the 5-HT3 receptor both *in vivo* and *in vitro*.

Another clear illustration of the role of serotonin in regulating auditory plasticity is in a well-established model of associative plasticity in frequency tuning of single neurons in auditory cortex. In addition to diminishing tone-evoked responses, serotonin alters the single-neuron response to a conditioning stimulus consisting of tones paired with electrical shock (Ji and Suga, 2007). The nature of the effect is dependent on the dose of serotonin administered by placement on the surface of the cortex. A low dose of serotonin (4 mM) shifts the best frequency of the neurons towards the conditioning frequency when the conditioning stimulus is paired with shock in a 15-min protocol. A higher dose of serotonin (20 mM) not only causes no shift in best frequency, but also reduces the extent and duration of a shift in best frequency evoked by a longer exposure to the conditioning paradigm. An agonist of 5-HT2 receptor facilitates the shifts in best frequency towards the conditioning stimulus, while an antagonist induces shifts away from the conditioning frequency. These findings suggest that serotonin facilitates conditioning-induced shifts in best frequency through 5-HT2 receptors, but that higher doses of serotonin activate additional receptor mechanisms that oppose these effects.

These studies demonstrate that serotonin can modulate multiple forms of auditory plasticity. It would not be surprising if serotonin modified additional forms of plasticity that have been reported in the auditory system.

4.3. How does serotonin change auditory processing?

Proposed functions for serotonin in auditory processing are diverse and generally vary with the nucleus of interest. In the gerbil LSO slice preparation, the application of serotonin suppresses evoked postsynaptic currents, but suppresses excitatory postsynaptic currents (EPSCs) evoked by the stimulation of ipsilateral afferents from the CN far more than IPSCs evoked by stimulation of the ipsilateral medial nucleus of the trapezoid body (MNTB) (Fitzgerald and Sanes, 1999). Such a change in the balance of excitatory and inhibitory inputs could lead to altered tuning for interaural level differences in the LSO.

In the IC *in vivo* preparation of bat and mouse, one focus has been on changes in the selectivity of responses to tones of different frequencies. The effects of serotonin on frequency tuning, whether they are suppressive or facilitatory, vary among neurons. Serotonin causes proportionally similar changes in spike count across the entire tuning range of some neurons, and sharply frequency-selective changes in spike count in other neurons (Hurley and Pollak, 2001; Hurley et al., 2008). Either type of change can alter the absolute bandwidth of sound to which an individual neuron can respond, suggesting that serotonin consequently regulates the representation of frequency across the tonotopic map of the IC. Because the suppressive effects of serotonin predominate in the IC (Hurley and Pollak, 1999, 2001), serotonin usually creates a greater selectivity in response. These changes in tuning have been associated with parallel increases in selectivity for more complex stimuli such as recorded species-specific vocalizations (Hurley and Pollak, 2005b). Perhaps not surprisingly, however, sounds that are acoustically rich in frequency or amplitude modulation are also associated with the most complex effects of serotonin observed. The influence of serotonin on responses to FM sweeps and recorded vocalizations can encompass both suppression and facilitation even for single neurons, depending on the spectrotemporal structure of the stimulus (Fig. 4; Hurley and Pollak, 1999, 2005a). This illustrates that the function of serotonin may not be easily inferred from elementary stimulus paradigms.

In the MGN of cat and guinea pig, serotonin does something quite different. It facilitates the transition from burst-firing mode to 'relay' mode by reducing burst firing in response to barrages of inhibitory inputs (Pape and McCormick, 1989; McCormick and Pape, 1990). This may contribute to a physiological state more sensitive to sensory input as serotonin levels increase in awake animals.

If a general statement can capture the influence of serotonin in all of these auditory nuclei, it is that serotonin changes the functional response properties of auditory neurons, through a shift in the balance of excitatory and inhibitory inputs or through a change in excitability. Whether serotonergic alteration of different response properties at multiple levels of the auditory neuraxis can be integrated into a single concept of serotonergic function has not been adequately explored.

5. Metamodulation

Summary: The infrastructure of the serotonergic system is subject to plasticity that is dependent on factors associated with auditory dysfunction, including age and trauma.

One of the most interesting aspects of serotonergic plasticity in the auditory system is that the infrastructure of the serotonergic system is itself subject to regulation, a phenomenon that has been called 'metamodulation' (Edwards et al., 2002; Mesce, 2002). Such plasticity has been captured in direct measurements of the expression of 5-HT receptors and density of serotonergic fibers, or indirectly through measurements of serotonergic availability and turnover. According to measurements of both types, serotonergic infrastructure within the auditory system is exceedingly malleable, an observation that has interesting implications for auditory adaptability and dysfunction. Factors that influence the serotonergic infrastructure in the auditory system include age, cochlear damage, and previous experience.

Age is a factor that influences the neurochemistry of the auditory system in multiple ways, including the availability of serotonin. In all subregions of the cochlear nucleus of rats, serotonin and 5-HIAA are higher in rats at 21 and 24 months than at 4 months (Cransac et al., 1996). This was proposed to be a compensatory mechanism triggered by age-related declines in 5-HT receptors or changes in other neurotransmitter systems. Specific types of serotonin receptors are also sensitive to aging. In both the cochlea and IC of mice, the expression of the 5-HT2B receptor increases in old mice with hearing loss (average age 32.4 months) relative to younger mice (average age 3 months: Tadros et al., 2007). Further, the individual levels of expression are correlated with measures of hearing such as ABR thresholds at some frequencies. The expression of 5-HT2B protein correspondingly increases in the IC of old mice, notably in a subpopulation of large stellate cells in the ventral regions of the central nucleus and in the external cortex. Instead of compensatory changes, these findings were interpreted by the

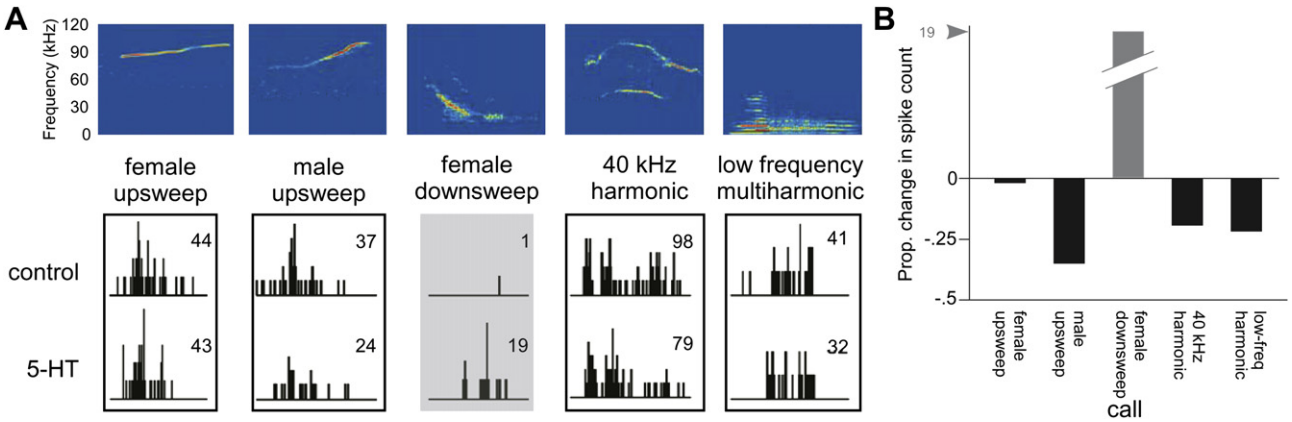

Fig. 4. Effects of serotonin (5-HT) on vocalization responses of IC neurons in mice can be stimulus-dependent. A) Responses of a single neuron to five recorded vocalizations (spectrograms at top) provided by CV Portfors. Responses to 4 of the five calls were mildly suppressed or not influenced by serotonin (open boxes), but responses to the female downsweep were strongly facilitated (gray box). Descriptions of the behavioral significance of the calls can be found in Holmstrom et al. (2010). B) Comparison of the proportional changes in spike count evoked by serotonin for each of the five calls.

authors as supporting a role for 5-HT2B receptors in contributing to age-related auditory dysfunction through multiple potential mechanisms including increased inflammation, changes in microcirculation or mitochondrial function, or increases in calcium levels.

Damage to the cochlea caused by physical or acoustic trauma can further change the expression or function of 5-HT receptors. Two separate 5-HT receptor subtypes in the IC, the 5-HT2C and 5-HT5B receptors, change in expression in opposite ways following cochlear ablation (Holt et al., 2005). The expression of 5-HT2C receptors (which facilitate tone-evoked responses in the IC: see above) is increased at 3, 21, and 90 days following cochlear ablation relative to animals with unablated cochleae. In contrast, the change in expression of 5-HT5B receptors is more transient, declining at 3 and 21 days following ablation, but returning to baseline levels at 90 days. These shifts in expression are part of a coordinated suite of changes in the expression of other genes, including a set of other neurotransmitter-related genes. A pilot study suggests that a less extreme form of damage to the cochlea, acoustic trauma, may also change serotonergic infrastructure in the IC, reducing the density of serotonergic fibers (M. Papesh, unpublished data).

In addition to events that substantially influence hearing such as aging or trauma to the cochlea, there is preliminary evidence that behavioral experience can alter the function of the serotonergic system in the IC (Hall et al., 2011). As described in an earlier section, serotonin in the IC of resident mice presented with an intruder increases over the course of the social interaction. After experiencing this paradigm once, mice show a larger serotonergic response when paired with a new intruder one week later. The aspects of the social experience and the mechanisms that trigger this change are unknown. However, this result suggests that changes in serotonergic infrastructure in the auditory system can be relatively rapid (days), and can occur in response to specific events.

6. Models of serotonergic function in the auditory system

All available evidence indicates that serotonergic projections within the auditory system comprise a complex and plastic system that has an important regulatory influence on auditory processing. The basic principles by which serotonin modulates auditory processing are similar to those that have been observed in motor systems in a wide range of animals for decades. As in motor systems, serotonin release in the auditory system is triggered by behaviorally important cues, and serotonin achieves selective effects by acting on specific cell types that express particular serotonin receptors and effector proteins to produce adaptive changes in behavior (Kiehn and Harris-Warrick, 1992; Zhang and Harris-Warrick, 1994; Katz, 1998; Sakurai et al., 2006; Viemari and Tryba, 2009; Harris-Warrick and Johnson, 2010). Despite, or perhaps even because of, the increasing characterization of the diversity of serotonergic effectors and effects within the auditory system, the question remains: what does serotonin do? As Fig. 5 visually summarizes, the serotonergic system integrates information on the current behavioral situation, internal state, and past experience. This information is then communicated to auditory neurons through short-term changes in the availability of serotonin and by longer-term regulation of serotonergic infrastructure. Auditory neurons respond to these changes with altered selectivity for auditory stimuli and cellular plasticity based on the selective expression of an array of different types of serotonin receptor.

Roles that serotonin might play in particular types of behavioral contexts are suggested by complementary sets of evidence from multiple studies. One such role is optimization of auditory responses during generally stressful or behaviorally arousing situations, including social interaction. Exposure to stress-inducing stimuli including noise, restricted movement, and electrical shock increase serotonin levels within multiple regions of the auditory system (Stark and Scheich, 1997; Cransac et al., 1998; Hall et al., 2010). At a cellular level, local changes in serotonin availability, or the activation of serotonin receptors, can influence neural coding and behavior. For example, the application of serotonin to auditory cortex during associative fear conditioning leads to stimulus-specific alterations in frequency tuning and presumably in the tonotopic map that may relate to adaptive learning (Ji and Suga, 2007) and the local manipulation of serotonin receptors in the IC influences aversive behavioral responses to the stimulation of this nucleus (Melo and Brandão, 1995). Social interactions are an interesting subset of serotonin-increasing behavioral conditions. Such interactions are associated in many vertebrate species with the production of vocalizations (for example, Holy and Guo, 2005; White et al., 2006; Knudsen and Gentner, 2010), and also with an increase in serotonin in at least one auditory nucleus, the IC, that selectively processes species-specific vocalizations (Klug et al., 2002; Holmstrom et al., 2010; Hall et al., 2011). At the level of single neurons, serotonin changes the responses of many IC neurons for such vocalizations in a way that could contribute to increased neural selectivity (Hurley and Pollak, 2005a). In assessing these specific functional scenarios, an outstanding issue is whether the selective short- or long-term changes in auditory processing that have been observed are adaptive, in the sense that they preserve auditory information that is salient to a given behavioral situation and/or de-emphasize nonsalient information.

Multiple authors have noted the role that this serotonergic regulatory process could play in auditory dysfunction. Serotonin has been advanced as a causal factor in auditory disorders with affective components, such as tinnitus and hyperacusis (Marriage and Barnes, 1995; Simpson and Davies, 2000), or as the cause of auditory symptoms in primarily affective disorders such as depression and schizophrenia (Johnson et al., 1998; Hegerl et al., 2001). In these models, plasticity in the serotonergic system, induced by trauma to the cochlea or through central affective dysfunction, alters serotonergic regulation of the balance between excitation and inhibition, resulting in symptoms such as phantom

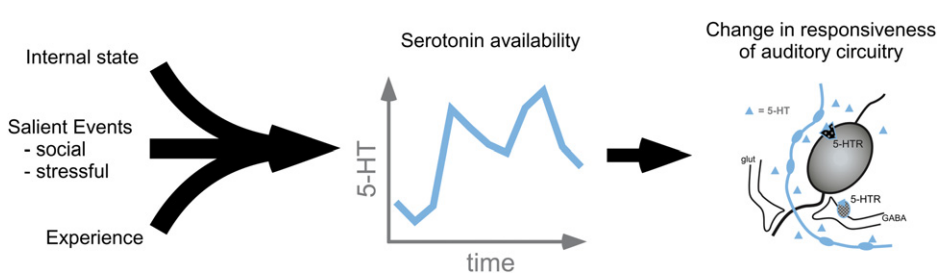

Fig. 5. Graphical abstract of context-dependent modulation of auditory processing by serotonin. Changes in internal state, external events such as social interaction or stressors, and experience all influence serotonin availability within the auditory system. Serotonin in turn modulates auditory neural circuitry.

sounds, excessive auditory gain, or reduced auditory filtering (Johnson et al., 1998; Hegerl et al., 2001; Robinson, 2007). Although clinical studies provide fairly rich evidence of some of the perceptual effects of serotonin, fewer behavioral studies have been performed in animal models to test the proposed mechanisms of these effects (but see Liu et al., 2003; Holt et al., 2005; Tadros et al., 2007).

The work described in this review provides a broad outline of an auditory regulatory system that is important in imparting information on behavioral context to auditory processing, but also illustrates substantial gaps in this outline. Further, serotonin can be viewed as only one exemplar of the wide range of neurochemicals capable of regulating auditory processing according to behavioral context, as illustrated by other articles in this issue. Indeed, other neuromodulators, such as norepinephrine, have effects that are comparable to those of serotonin within the auditory system, even intersecting with serotonin at specific effectors (Pape and McCormick, 1989; Manunta and Edeline, 1997, 2004; Hurley et al., 2004). Auditory plasticity is therefore likely influenced by many signaling molecules that impart different types of non-auditory information and may interact in linear or nonlinear ways. In addition to further characterizing the nature of serotonergic influence in auditory processing, a future challenge in characterizing the state-dependence of auditory processing will be establishing the behavioral salience of, and interactions among, different chemical regulatory systems.

Acknowledgments

The authors would like to thank Dr. Ann Thompson for helpful comments on the manuscript. This work is dedicated to Dr. Donald Gans, who made a number of the physiological studies reviewed here possible.

References

Abrams, J.K., Johnson, P.L., Hollis, J.H., Lowry, C.A., 2004. Anatomic and functional topography of the dorsal raphe nucleus. Ann. N. Y Acad. Sci. 1018, 46–57.

Adell, A., Celada, P., Abellan, M.T., Artigas, F., 2002. Origin and functional role of the extracellular serotonin in the midbrain raphe nuclei. Brain Res. Brain Res. Rev. 39, 154–180.

Baldan Ramsey, L.C., Sinha, S.R., Hurley, L.M., 2010. 5-HT1A and 5-HT1B receptors differentially modulate rate and timing of auditory responses in the mouse inferior colliculus. Eur. J. Neurosci. 32, 368–379.

Barnes, N.M., Sharp, T., 1999. A review of central 5-HT receptors and their function. Neuropharmacology 38, 1083–1152.

Basura, G.J., Abbas, A.I., O'Donohue, H., Lauder, J.M., Roth, B.L., Walker, P.D., Manis, P.B., 2008. Ontogeny of serotonin and serotonin2A receptors in rat auditory cortex. Hear. Res. 244, 45–50.

Beaudet, A., Descarries, L., 1981. The fine structure of central serotonin neurons. J. Physiol. (Paris) 77, 193–203.

Bohorquez, A., Hurley, L.M., 2009. Activation of serotonin 3 receptors changes *in vivo* auditory responses in the mouse inferior colliculus. Hear. Res. 251, 29–38.

Boutelle, M.G., Zetterstrom, T., Pei, Q., Svensson, L., Fillenz, M., 1990. *In vivo* neurochemical effects of tail pinch. J. Neurosci. Methods 34, 151–157.

Bunin, M.A., Wightman, R.M., 1998. Quantitative evaluation of 5-hydroxytryptamine (serotonin) neuronal release and uptake: an investigation of extrasynaptic transmission. J. Neurosci. 18, 4854–4860.

Campbell, M.J., Lewis, D.A., Foote, S.L., Morrison, J.H., 1987. Distribution of choline acetyltransferase-, serotonin-, dopamine-beta-hydroxylase-, tyrosine hydroxylase-immunoreactive fibers in monkey primary auditory cortex. J. Comp. Neurol. 261, 209–220.

Celada, P., Artigas, F., 1993. Monoamine oxidase inhibitors increase preferentially extracellular 5-hydroxytryptamine in the midbrain raphe nuclei. A brain microdialysis study in the awake rat. Naunyn Schmiedebergs Arch. Pharmacol. 347, 583–590.

Chalmers, D.T., Watson, S.J., 1991. Comparative anatomical distribution of 5-HT1A receptor mRNA and 5-HT1A binding in rat brain—a combined in situ hybridisation/*in vitro* receptor autoradiographic study. Brain Res. 561, 51–60.

Clement, H.W., Kirsch, M., Hasse, C., Opper, C., Gemsa, D., Wesemann, W., 1998. Effect of repeated immobilization on serotonin metabolism in different rat brain areas and on serum corticosterone. J. Neural Transm. 105, 1155–1170.

Cransac, H., Cottet-Emard, J.M., Pequignot, J.M., Peyrin, L., 1995. Monoamines (noradrenaline, dopamine, serotonin) in the rat cochlear nuclei: endogenous levels and turnover. Hear. Res. 90, 65–71.

Cransac, H., Cottet-Emard, J.M., Hellstrom, S., Peyrin, L., 1998. Specific sound-induced noradrenergic and serotonergic activation in central auditory structures. Hear. Res. 118, 151–156.

Cransac, H., Peyrin, L., Cottet-Emard, J.M., Farhat, F., Pequignot, J.M., Reber, A., 1996. Aging effects on monoamines in rat medial vestibular and cochlear nuclei. Hear. Res. 100, 150–156.

Cuccurazzu, B., Halberstadt, A.L., 2008. Projections from the vestibular nuclei and nucleus prepositus hypoglossi to dorsal raphe nucleus in rats. Neurosci. Lett. 439, 70–74.

Dahlin, A., Xia, L., Kong, W., Hevner, R., Wang, J., 2007. Expression and immunolocalization of the plasma membrane monoamine transporter in the brain. Neuroscience 146, 1193–1211.

DeFelipe, J., Hendry, S.H., Hashikawa, T., Jones, E.G., 1991. Synaptic relationships of serotonin-immunoreactive terminal baskets on GABA neurons in the cat auditory cortex. Cereb. Cortex 1, 117–133.

Ebert, U., Ostwald, J., 1992. Serotonin modulates auditory information processing in the cochlear nucleus of the rat. Neurosci. Lett. 145, 51–54.

Edagawa, Y., Saito, H., Abe, K., 2001. Endogenous serotonin contributes to a developmental decrease in long-term potentiation in the rat visual cortex. J. Neurosci. 21, 1532–1537.

Edwards, D.H., Yeh, S.R., Musolf, B.E., Antonsen, B.L., Krasne, F.B., 2002. Metamodulation of the crayfish escape circuit. Brain Behav. Evol. 60, 360–369.

Faingold, C.L., Gehlbach, G., Caspary, G.M., 1991. Functional pharmacology of inferior colliculus neurons. In: Altschuler, R.A. (Ed.), Neurobiology of Hearing: The Central Auditory System. Raven, New York, pp. 223–251.

Fitzgerald, K.K., Sanes, D.H., 1999. Serotonergic modulation of synapses in the developing gerbil lateral superior olive. J. Neurophysiol. 81, 2743–2752.

Fitzpatrick, D., Diamond, I.T., Raczkowski, D., 1989. Cholinergic and monoaminergic innervation of the cat's thalamus: comparison of the lateral geniculate nucleus with other principal sensory nuclei. J. Comp. Neurol. 288, 647–675.

Gasser, P.J., Orchinik, M., Raju, I., Lowry, C.A., 2009. Distribution of organic cation transporter 3, a corticosterone-sensitive monoamine transporter, in the rat brain. J. Comp. Neurol. 512, 529–555.

Gil-Loyzaga, P., Bartolome, M.V., Vicente-Torres, M.A., 1997. Serotonergic innervation of the organ of Corti of the cat cochlea. Neuroreport 8, 3519–3522.

Grahn, R.E., Will, M.J., Hammack, S.E., Maswood, S., McQueen, M.B., Watkins, L.R., Maier, S.F., 1999. Activation of serotonin-immunoreactive cells in the dorsal raphe nucleus in rats exposed to an uncontrollable stressor. Brain Res. 826, 35–43.

Gu, Q., 2002. Neuromodulatory transmitter systems in the cortex and their role in cortical plasticity. Neuroscience 111, 815–835.

Hall, I.C., Rebec, G.V., Hurley, L.M., 2010. Serotonin in the inferior colliculus fluctuates with behavioral state and environmental stimuli. J. Exp. Biol. 213, 1009–1017.

Hall, I.C., Sell, G.L., Hurley, L.M., 2011. Social regulation of serotonin in the auditory midbrain. Behav. Neurosci., in press.

Hannon, J., Hoyer, D., 2008. Molecular biology of 5-HT receptors. Behav. Brain Res. 195, 198–213.

Harris-Warrick, R.M., Johnson, B.R., 2010. Checks and balances in neuromodulation. Front. Behav. Neurosci. 4.

Hayley, S., Borowski, T., Merali, Z., Anisman, H., 2001. Central monoamine activity in genetically distinct strains of mice following a psychogenic stressor: effects of predator exposure. Brain Res. 892, 293–300.

Hegerl, U., Gallinat, J., Juckel, G., 2001. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J. Affect. Disord. 62, 93–100.

Heym, J., Steinfels, G.F., Jacobs, B.L., 1982. Activity of serotonin-containing neurons in the nucleus raphe pallidus of freely moving cats. Brain Res. 251, 259–276.

Holt, A.G., Asako, M., Lomax, C.A., MacDonald, J.W., Tong, L., Lomax, M.I., Altschuler, R.A., 2005. Deafness-related plasticity in the inferior colliculus: gene expression profiling following removal of peripheral activity. J. Neurochem. 93, 1069–1086.

Holmstrom, L.A., Eeuwes, L.B., Roberts, P.D., Portfors, C.V., 2010. Efficient encoding of vocalizations in the auditory midbrain. J. Neurosci. 30, 802–819.

Holy, T.E., Guo, Z., 2005. Ultrasonic songs of male mice. PLoS Biol. 3, e386.

Hoyer, D., Hannon, J.P., Martin, G.R., 2002. Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol. Biochem. Behav. 71, 533–554.

Hurley, L.M., 2006. Different serotonin receptor agonists have distinct effects on sound-evoked responses in inferior colliculus. J. Neurophysiol. 96, 2177–2188.

Hurley, L.M., 2007. Activation of the serotonin 1A receptor alters the temporal characteristics of auditory responses in the inferior colliculus. Brain Res. 1181, 21–29.

Hurley, L.M., Park, T., Brand, A., Grothe, B., 2003. *In vivo* neuromodulation of LSO neurons ARO Abstr #1247.

Hurley, L.M., Pollak, G.D., 1999. Serotonin differentially modulates responses to tones and frequency-modulated sweeps in the inferior colliculus. J. Neurosci. 19, 8071–8082.

Hurley, L.M., Pollak, G.D., 2001. Serotonin effects on frequency tuning of inferior colliculus neurons. J. Neurophysiol. 85, 828–842.

Hurley, L.M., Thompson, A.M., 2001. Serotonergic innervation of the auditory brainstem of the Mexican free-tailed bat, Tadarida brasiliensis. J. Comp. Neurol. 435, 78–88.

Hurley, L.M., Pollak, G.D., 2005a. Serotonin shifts first-spike latencies of inferior colliculus neurons. J. Neurosci. 25, 7876–7886.
Hurley, L.M., Pollak, G.D., 2005b. Serotonin modulates responses to species-specific vocalizations in the inferior colliculus. J. Comp. Physiol. A Neuroethol Sens Neural Behav. Physiol. 191, 535–546.
Hurley, L.M., Devilbiss, D.M., Waterhouse, B.D., 2004. A matter of focus: monoaminergic modulation of stimulus coding in mammalian sensory networks. Curr. Opin. Neurobiol. 14, 488–495.
Hurley, L.M., Tracy, J.A., Bohorquez, A., 2008. Serotonin 1B receptor modulates frequency response curves and spectral integration in the inferior colliculus by reducing GABAergic inhibition. J. Neurophysiol. 100, 1656–1667.
Jacobs, B.L., Azmitia, E.C., 1992. Structure and function of the brain serotonin system. Physiol. Rev. 72, 165–229.
Jacobs, B.L., Fornal, C.A., 1999. Activity of serotonergic neurons in behaving animals. Neuropsychopharmacology 21, 9S–15S.
Ji, W., Suga, N., 2007. Serotonergic modulation of plasticity of the auditory cortex elicited by fear conditioning. J. Neurosci. 27, 4910–4918.
Johnson, R.G., Stevens, K.E., Rose, G.M., 1998. 5-Hydroxytryptamine2 receptors modulate auditory filtering in the rat. J. Pharmacol. Exp. Ther. 285, 643–650.
Kaiser, A., Covey, E., 1997. 5-HT innervation of the auditory pathway in birds and bats. In: Syka, J.L. (Ed.), Acoustical Signal Processing in the Central Auditory System. Plenum, New York, pp. 71–78.
Katz, P.S., 1998. Neuromodulation intrinsic to the central pattern generator for escape swimming in Tritonia. Ann. N. Y. Acad. Sci. 860, 181–188.
Kawano, H., Decker, K., Reuss, S., 1996. Is there a direct retina-raphe-suprachiasmatic nucleus pathway in the rat? Neurosci. Lett. 212, 143–146.
Kiehn, O., Harris-Warrick, R.M., 1992. Serotonergic stretch receptors induce plateau properties in a crustacean motor neuron by a dual-conductance mechanism. J. Neurophysiol. 68, 485–495.
Kim, D.O., Yang, X.M., Ye, Y., 2003. A subpopulation of dorsal raphe nucleus neurons retrogradely labeled with cholera toxin-B injected into the inner ear. Exp. Brain Res. 153, 514–521.
Klepper, A., Herbert, H., 1991. Distribution and origin of noradrenergic and serotonergic fibers in the cochlear nucleus and inferior colliculus of the rat. Brain Res. 557, 190–201.
Klug, A., Bauer, E.E., Hanson, J.T., Hurley, L., Meitzen, J., Pollak, G.D., 2002. Response selectivity for species-specific calls in the inferior colliculus of Mexican free-tailed bats is generated by inhibition. J. Neurophysiol. 88, 1941–1954.
Knudsen, D.P., Gentner, T.Q., 2010. Mechanisms of song perception in oscine birds. Brain Lang.
Kosofsky, B.E., Molliver, M.E., 1987. The serotoninergic innervation of cerebral cortex: different classes of axon terminals arise from dorsal and median raphe nuclei. Synapse 1, 153–168.
Kranz, G.S., Kasper, S., Lanzenberger, R., 2010. Reward and the serotonergic system. Neurosci 166, 1023–1035.
Lavoie, B., Parent, A., 1991. Serotoninergic innervation of the thalamus in the primate: an immunohistochemical study. J. Comp. Neurol. 312, 1–18.
Le Moal, M., Olds, M.E., 1979. Peripheral auditory input to the midbrain limbic area and related structures. Brain Res. 167, 1–17.
Lee, H.S., Kim, M.A., Valentino, R.J., Waterhouse, B.D., 2003. Glutamatergic afferent projections to the dorsal raphe nucleus of the rat. Brain Res. 963, 57–71.
Lewis, D.A., Campbell, M.J., Foote, S.L., Morrison, J.H., 1986. The monoaminergic innervation of primate neocortex. Hum. Neurobiol. 5, 181–188.
Liu, J., Li, X., Wang, L., Dong, Y., Han, H., Liu, G., 2003. Effects of salicylate on serotoninergic activities in rat inferior colliculus and auditory cortex. Hear. Res. 175, 45–53.
Liu, S., Bubar, M.J., Lanfranco, M.F., Hillman, G.R., Cunningham, K.A., 2007. Serotonin2C receptor localization in GABA neurons of the rat medial prefrontal cortex: implications for understanding the neurobiology of addiction. Neuroscience 146, 1677–1688.
Luo, X., Persico, A.M., Lauder, J.M., 2003. Serotonergic regulation of somatosensory cortical development: lessons from genetic mouse models. Dev. Neurosci. 25, 173–183.
Manunta, Y., Edeline, J.M., 1997. Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. Eur. J. Neurosci. 9, 833–847.
Manunta, Y., Edeline, J.M., 2004. Noradrenergic induction of selective plasticity in the frequency tuning of auditory cortex neurons. J. Neurophysiol. 92, 1445–1463.
Marriage, J., Barnes, N.M., 1995. Is central hyperacusis a symptom of 5-hydroxytryptamine (5-HT) dysfunction? J. Laryngol. Otol. 109, 915–921.
Mas, M., Fumero, B., Fernandez-Vera, J.R., Gonzalez-Mora, J.L., 1995. Neurochemical correlates of sexual exhaustion and recovery as assessed by *in vivo* microdialysis. Brain Res. 675, 13–19.
McCormick, D.A., Pape, H.C., 1990. Noradrenergic and serotonergic modulation of a hyperpolarization-activated cation current in thalamic relay neurones. J. Physiol. 431, 319–342.
Melo, L.L., Brandão, M.L., 1995. Role of 5-HT1A and 5-HT2 receptors in the aversion induced by electrical stimulation of inferior colliculus. Pharmacol. Biochem. Behav. 51, 317–321.
Mendlin, A., Martin, F.J., Rueter, L.E., Jacobs, B.L., 1996. Neuronal release of serotonin in the cerebellum of behaving rats: an *in vivo* microdialysis study. J. Neurochem. 67, 617–622.
Mesce, K.A., 2002. Metamodulation of the biogenic amines: second-order modulation by steroid hormones and amine cocktails. Brain Behav. Evol. 60, 339–349.
Miko, I.J., Sanes, D.H., 2009. Transient gain adjustment in the inferior colliculus is serotonin- and calcium-dependent. Hear. Res. 251, 39–50.
Mitsushima, D., Yamada, K., Takase, K., Funabashi, T., Kimura, F., 2006. Sex differences in the basolateral amygdala: the extracellular levels of serotonin and dopamine, and their responses to restraint stress in rats. Eur. J. Neurosci. 24, 3245–3254.
Mizutani, H., Hori, T., Takahashi, T., 2006. 5-HT1B receptor-mediated presynaptic inhibition at the calyx of Held of immature rats. Eur. J. Neurosci. 24, 1946–1954.
Monckton, J.E., McCormick, D.A., 2002. Neuromodulatory role of serotonin in the ferret thalamus. J. Neurophysiol. 87, 2124–2136.
Müller, C.P., De Souza Silva, M.A., Huston, J.P., 2007. Double dissociating effects of sensory stimulation and cocaine on serotonin activity in the occipital and temporal cortices. Neuropharmacology 52, 854–862.
Papadopoulos, G.C., Parnavelas, J.G., 1991. Monoamine systems in the cerebral cortex: evidence for anatomical specificity. Prog. Neurobiol. 36, 195–200.
Pape, H.C., McCormick, D.A., 1989. Noradrenaline and serotonin selectively modulate thalamic burst firing by enhancing a hyperpolarization-activated cation current. Nature 340, 715–718.
Peroutka, S.J., 1994. Molecular biology of serotonin (5-HT) receptors. Synapse 18, 241–260.
Peroutka, S.J., 1995. 5-HT receptors: past, present and future. Trends Neurosci. 18, 68–69.
Peruzzi, D., Dut, A., 2004. GABA, serotonin and serotonin receptors in the rat inferior colliculus. Brain Res. 998, 247–250.
Peyron, C., Petit, J.M., Rampon, C., Jouvet, M., Luppi, P.H., 1998. Forebrain afferents to the rat dorsal raphe nucleus demonstrated by retrograde and anterograde tracing methods. Neurosci 82, 443–468.
Pompeiano, M., Palacios, J.M., Mengod, G., 1992. Distribution and cellular localization of mRNA coding for 5-HT1A receptor in the rat brain: correlation with receptor binding. J. Neurosci. 12, 440–453.
Pompeiano, M., Palacios, J.M., Mengod, G., 1994. Distribution of the serotonin 5-HT2 receptor family mRNAs: comparison between 5-HT2A and 5-HT2C receptors. Brain Res. Mol. Brain Res. 23, 163–178.
Portas, C.M., Bjorvatn, B., Ursin, R., 2000. Serotonin and the sleep/wake cycle: special emphasis on microdialysis studies. Prog. Neurobiol. 60, 13–35.
Pum, M.E., Huston, J.P., De Souza Silva, M.A., Muller, C.P., 2008. Visual sensory-motor gating by serotonin activation in the medial prefrontal and occipital, but not in the rhinal, cortices in rats. Neuroscience 153, 361–372.
Rao, D., Basura, G.J., Roche, J., Daniels, S., Mancilla, J.G., Manis, P.B., 2010. Hearing loss alters serotonergic modulation of intrinsic excitability in auditory cortex. J. Neurophysiol. 104, 2693–2703.
Robinson, S., 2007. Antidepressants for treatment of tinnitus. Prog. Brain Res. 166, 263–271.
Rueter, L.E., Jacobs, B.L., 1996. A microdialysis examination of serotonin release in the rat forebrain induced by behavioral/environmental manipulations. Brain Res. 739, 57–69.
Sakurai, A., Darghouth, N.R., Butera, R.J., Katz, P.S., 2006. Serotonergic enhancement of a 4-AP-sensitive current mediates the synaptic depression phase of spike timing-dependent neuromodulation. J. Neurosci. 26, 2010–2021.
Sari, Y., 2004. Serotonin1B receptors: from protein to physiological function and behavior. Neurosci. Biobehav. Rev. 28, 565–582.
Simpson, J.J., Davies, W.E., 2000. A review of evidence in support of a role for 5-HT in the perception of tinnitus. Hear. Res. 145, 1–7.
Smith, D.G., Davis, R.J., Gehlert, D.R., Nomikos, G.G., 2006. Exposure to predator odor stress increases efflux of frontal cortex acetylcholine and monoamines in mice: comparisons with immobilization stress and reversal by chlordiazepoxide. Brain Res. 1114, 24–30.
Stark, H., Scheich, H., 1997. Dopaminergic and serotonergic neurotransmission systems are differentially involved in auditory cortex learning: a long-term microdialysis study of metabolites. J. Neurochem. 68, 691–697.
Steinbusch, H.W., 1981. Distribution of serotonin-immunoreactivity in the central nervous system of the rat-cell bodies and terminals. Neurosci 6, 557–618.
Tadros, S.F., D'Souza, M., Zettel, M.L., Zhu, X., Lynch-Erhardt, M., Frisina, R.D., 2007. Serotonin 2B receptor: upregulated with age and hearing loss in mouse auditory system. Neurobiol. Aging 28, 1112–1123.
Takase, L.F., Nogueira, M.I., 2008. Patterns of fos activation in rat raphe nuclei during feeding behavior. Brain Res. 1200, 10–18.
Thompson, A.M., 2006. Non-serotonergic lateral superior olivary neurons of the neonatal mouse contain serotonin. Brain Res. 1122, 122–125.
Thompson, A.M., Schofield, B.R., 2000. Afferent projections of the superior olivary complex. Microsc. Res. Tech. 51, 330–354.
Thompson, A.M., Thompson, G.C., 2001. Serotonin projection patterns to the cochlear nucleus. Brain Res. 907, 195–207.
Thompson, A.M., Wiechmann, A.F., 2002. 5-HT(1A) receptor subtype mRNA expression in cochlear nucleus. Hear. Res. 164, 77–81.
Thompson, A.M., Hurley, L.M., 2004. Dense serotonergic innervation of principal nuclei of the superior olivary complex in mouse. Neurosci. Lett. 356, 179–182.
Thompson, A.M., Thompson, G.C., 2009. Experimental evidence that the serotonin transporter mediates serotonin accumulation in LSO neurons of the postnatal mouse. Brain Res. 1253, 60–68.
Thompson, A.M., Moore, K.R., Thompson, G.C., 1995. Distribution and origin of serotoninergic afferents to guinea pig cochlear nucleus. J. Comp. Neurol. 351, 104–116.

Thompson, G.C., Thompson, A.M., Garrett, K.M., Britton, B.H., 1994. Serotonin and serotonin receptors in the central auditory system. Otolaryngol. Head Neck Surg. 110, 93–102.
To, Z.P., Bonhaus, D.W., Eglen, R.M., Jakeman, L.B., 1995. Characterization and distribution of putative 5-ht7 receptors in guinea-pig brain. Br. J. Pharmacol. 115, 107–116.
Trulson, M.E., 1985. Simultaneous recording of dorsal raphe unit activity and serotonin release in the striatum using voltammetry in awake, behaving cats. Life Sci. 37, 2199–2204.
Vahabzadeh, A., Fillenz, M., 1994. Comparison of stress-induced changes in noradrenergic and serotonergic neurons in the rat hippocampus using microdialysis. Eur. J. Neurosci. 6, 1205–1212.
Vergé, D., Calas, A., 2000. Serotoninergic neurons and serotonin receptors: gains from cytochemical approaches. J. Chem. Neuroanat. 18, 41–56.
Vertes, R.P., Linley, S.B., Hoover, W.B., 2010. Pattern of distribution of serotonergic fibers to the thalamus of the rat. Brain Struct. Funct. 215, 1–28.
Viemari, J.C., Tryba, A.K., 2009. Bioaminergic neuromodulation of respiratory rhythm *in vitro*. Respir. Physiol. Neurobiol. 168, 69–75.
Vu, D.H., Törk, I., 1992. Differential development of the dual serotoninergic fiber system in the cerebral cortex of the cat. J. Comp. Neurol. 317, 156–174.
Waeber, C., Sebben, M., Nieoullon, A., Bockaert, J., Dumuis, A., 1994. Regional distribution and ontogeny of 5-HT4 binding sites in rodent brain. Neuropharmacology 33, 527–541.
Wang, H.T., Luo, B., Huang, Y.N., Zhou, K.Q., Chen, L., 2008. Sodium salicylate suppresses serotonin-induced enhancement of GABAergic spontaneous inhibitory postsynaptic currents in rat inferior colliculus *in vitro*. Hear Res. 236, 42–51.
Wang, X., Robertson, D., 1997. Effects of bioamines and peptides on neurones in the ventral nucleus of trapezoid body and rostral periolivary regions of the rat superior olivary complex: an *in vitro* investigation. Hear Res. 106, 20–28.
Waterhouse, B.D., Devilbiss, D., Seiple, S., Markowitz, R., 2004. Sensorimotor-related discharge of simultaneously recorded, single neurons in the dorsal raphe nucleus of the awake, unrestrained rat. Brain Res. 1000, 183–191.
White, S.A., Fisher, S.E., Geschwind, D.H., Scharff, C., Holy, T.E., 2006. Singing mice, songbirds, and more: models for FOXP2 function and dysfunction in human speech and language. J. Neurosci. 26, 10376–10379.
Willard, F.H., Ho, R.H., Martin, G.F., 1984. The neuronal types and the distribution of 5-hydroxytryptamine and enkephalin-like immunoreactive fibers in the dorsal cochlear nucleus of the North American opossum. Brain Res. Bull. 12, 253–266.
Wright, D.E., Seroogy, K.B., Lundgren, K.H., Davis, B.M., Jennes, L., 1995. Comparative localization of serotonin1A, 1C, and 2 receptor subtype mRNAs in rat brain. J. Comp. Neurol. 351, 357–373.
Xiang, Z., Prince, D.A., 2003. Heterogeneous actions of serotonin on interneurons in rat visual cortex. J. Neurophysiol. 89, 1278–1287.
Ye, Y., Kim, D.O., 2001. Connections between the dorsal raphe nucleus and a hindbrain region consisting of the cochlear nucleus and neighboring structures. Acta Otolaryngol. 121, 284–288.
Zeng, S., Li, J., Zhang, X., Zuo, M., 2007. Distinction of neurochemistry between the cores and their shells of auditory nuclei in tetrapod species. Brain Behav. Evol. 70, 1–20.
Zhang, B., Harris-Warrick, R.M., 1994. Multiple receptors mediate the modulatory effects of serotonergic neurons in a small neural network. J. Exp. Biol. 190, 55–77.