Chapter 9
Circuits for Modulation of Auditory Function

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Abstract This chapter discusses anatomical, physiological, and functional aspects of circuits associated with four major neuromodulators: acetylcholine, serotonin, noradrenaline, and dopamine. These neuromodulators occur in nearly all auditory structures from the cochlea of the inner ear to the cortex of the brain. A review of the anatomy is focused on the origins of modulatory inputs to auditory structures and the patterns of termination in those areas. Sources of the modulatory inputs include widely recognized cell groups in the basal forebrain and pontomesencephalic tegmentum (for acetylcholine), raphe nuclei (for serotonin), locus coeruleus (for noradrenaline), and ventral tegmental area (for dopamine), as well as smaller cell groups in the brainstem. In addition, there are numerous examples of cells within the auditory system that release one or more of these neuromodulators. Physiology and function are discussed from several perspectives, starting with a brief overview of methods used for assessing modulatory function. Neuromodulators are directly involved in regulating auditory processing according to both internal state and stimulus salience. Many mechanisms are likely involved. Neuromodulators can reconfigure auditory circuitry through multiple receptor types and in multiple auditory regions. Furthermore, multiple neuromodulators may converge at the level of single neuron types. This makes the effects of neuromodulators complex but confers the ability to produce a range of behaviorally appropriate outputs from auditory circuitry. In addition, neuromodulators facilitate long-term plasticity. Such plasticity plays a role in many adaptive responses, including numerous changes that may play a role in the auditory dysfunction that follows hearing loss.

Keywords Acetylcholine · Behavioral context · Basal forebrain · Dopamine · Internal state · Laterodorsal tegmental nucleus · Locus coeruleus · Norepinephrine ·

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Nucleus basalis · Pedunculopontine tegmental nucleus · Plasticity · Raphe nuclei · Salience · Serotonin · Ventral tegmental area

9.1 Introduction

Neuromodulation of hearing refers to mechanisms that alter the way sounds are processed in auditory circuits. As a consequence, neuromodulators play important and varied roles in hearing, including mediating the effects of behavioral state and external events on auditory perception. Neuromodulation is also important for plasticity during development and learning as well as in response to damage or dysfunction of the nervous system.

There are many ways to define "neuromodulator" (see discussion by Descarries and Mechawar 2008) and recent interpretations include a growing list of interneuronal signaling molecules. Neuromodulators that act on auditory circuits include monoamines and acetylcholine as well as various peptides, including opioids, substance P, vasoactive intestinal polypeptide, and cholecystokinin, and gases such as nitric oxide. Even glutamate and GABA (gamma-aminobutyric acid) can be seen as neuromodulators in some circuits (e.g., Lee and Sherman 2010).

The following discussion focuses on four "conventional" neuromodulators: acetylcholine (ACh), serotonin (5-hydroxytryptamine or 5-HT), noradrenaline (NA or norepinephrine), and dopamine (DA)(all abbreviations in Table 9.1). Numerous neuroscience texts can provide relevant background. For example, Cooper et al. (2003) provide an overview of basic neuropharmacology (including synthesis, receptors, etc.) for each of the neuromodulators. The present and previous volumes in the Springer Handbook of Auditory Research series provide background on auditory circuits (e.g., Webster et al. 1992; Ryugo et al. 2011). In addition, Paxinos (1995) provides a useful introduction with detailed descriptions of many of the nuclei not usually considered in discussions of the traditional auditory pathways.

9.2 Anatomy of Modulatory Circuits

9.2.1 Common Properties of Modulatory Nuclei

Each of the modulatory systems discussed here is associated with one or more nuclei in the brainstem or basal forebrain. These nuclei are often diffusely organized with poorly defined boundaries that can vary between species. Moreover, while a nucleus can be associated with a particular modulator, that nucleus invariably contains neurons with a variety of neurotransmitter phenotypes. For example, the "cholinergic nuclei" of the basal forebrain contain cholinergic as well as glutamatergic and GABAergic cells. In some cases, the different phenotypes have different projections, but multiple phenotypes also can project to a single target. The fact that the different phenotypes are typically intermingled complicates both anatomical and physiological

Table 9.1 Abbreviations

5-HT	5-Hydroxytryptamine or serotonin
5-HT1B	Serotonin receptor type 1B
5-HT2A	Serotonin receptor type 2A
ACh	Acetylcholine
CA	Cerebral aqueduct
CG	Central gray of the midbrain
DA	Dopamine
DRN	Dorsal raphe nucleus
GABA	Gamma-aminobutyric acid
LC	Locus coeruleus
LDT	Laterodorsal tegmental nucleus
LPGi	Lateral paragigantocellular nucleus
MGm	Medial geniculate body, medial subdivision
MGv	Medial geniculate body, ventral subdivision
NA	Noradrenaline
NB	Nucleus basalis
PMT	Pontomesencephalic tegmentum
PPT	Pedunculopontine tegmental nucleus
VTA	Ventral tegmental area

studies because extra steps must be taken to attribute specific features (e.g., response properties, axonal projection patterns) to cells that use a specific neurotransmitter.

Another feature common among the modulatory nuclei is for a relatively small number of cells, from a few thousand up to tens of thousands, to innervate very wide expanses of the nervous system. Those numbers appear to apply across mammals; generally, the data are most complete for rats (Descarries and Mechawar 2008). Branching axonal projections play a role in some pathways, but the extent of branching varies between systems. Finally, there is evidence that some cells within the traditional auditory pathways make and release various modulators (although they are not always portrayed from that perspective). The best known example is the release of acetylcholine by olivocochlear cells. Some of these cells also have projections to the cochlear nucleus. Consequently, cholinergic effects in the cochlear nucleus must represent a combination of effects of cholinergic projections from auditory nuclei (i.e., the superior olivary complex) and cholinergic projections from the nonauditory cholinergic nuclei in the brainstem. Similar examples can be cited for dopaminergic projections. This issue emphasizes the likelihood that a given modulator serves a wide variety of functions.

9.2.2 Acetylcholine

Cholinergic cells are located in numerous brain regions including both brainstem and forebrain areas (Woolf 1991). Cholinergic innervation of the auditory system originates in four regions. Two such regions are associated with widespread

cholinergic innervation of the central nervous system: the basal forebrain (Sect. 9.2.2.1) and the pontomesencephalic tegmentum (PMT) (Sect. 9.2.2.2). The third region is within the superior olivary complex and is a source of cholinergic projections to lower auditory centers. The final region is a small nucleus of the reticular formation, the lateral paragigantocellular nucleus (LPGi; also known as the rostral ventrolateral medulla), that has close ties to auditory nuclei and other brainstem regions.

9.2.2.1 Cholinergic Groups in the Basal Forebrain

Cholinergic groups in the basal forebrain include the nucleus basalis, septal nuclei, and the vertical and horizontal limbs of the diagonal band. They have been associated with cognitive function and selective processing of sensory stimuli (Sarter and Bruno 1997). These cell groups provide the main sources of cholinergic input to the neocortex and may provide some cholinergic input to the thalamus (Descarries and Mechawar 2008; Varela 2014). The cholinergic innervation of the auditory cortex originates from this basal forebrain group, but the distribution of the cholinergic cells can vary across species. For example, in ferrets the majority of cells are located in nucleus basalis, but in cats the cells are distributed across the nucleus basalis and laterally into the putamen and globus pallidus (Kamke et al. 2005; Bajo et al. 2014).

Cholinergic axons terminate across auditory cortical areas and in all cortical layers, although the relative density varies with layer, cortical area, and species (Miller et al. 2013; Bajo et al. 2014). The available evidence suggests that cholinergic receptors are located on the cell bodies or dendrites of pyramidal and nonpyramidal cortical cells, on a variety of axon terminals within the cortex including ascending inputs from the thalamus, and on excitatory and inhibitory inputs from other cortical neurons (Metherate 2011; Edeline 2012).

9.2.2.2 Cholinergic Groups in the Pontomesencephalic Tegmentum

The PMT consists of the pedunculopontine tegmental nucleus (PPT) and the laterodorsal tegmental nucleus (LDT), which together are the main sources of cholinergic projections to the thalamus and the ventral tegmental area as well as numerous other brainstem regions. These widespread projections are associated with a variety of functions. As part of the ascending reticular activating system, the PMT has been associated with arousal (Woolf 1991; although see Fuller et al. 2011 for a discussion of arousal and glutamatergic versus cholinergic projections). Arousal and the related control of the sleep–wake cycle are often discussed in concert with PMT projections to the thalamus and the basal forebrain. The PMT is the primary source of cholinergic projections to the thalamus, although little attention has been focused on auditory nuclei (Steriade et al. 1988; Motts and Schofield 2010).

In general (across species and thalamic nuclei), the projections are bilateral with an ipsilateral predominance, and they originate from more cells in the PPT than in the LDT. Studies focused on the medial geniculate nucleus suggest possible species differences, with acetylcholine input arising only in the PPT in rats but in both PPT and LDT in guinea pigs (discussed in Motts and Schofield 2010). Whether the apparent difference is real or results from technical issues is unclear, but it highlights an unresolved issue about differences between the LDT and the PPT. It has been suggested on connectional grounds that the LDT is biased toward limbic circuits (Woolf 1991); the utility of this distinction remains to be determined.

The identity of thalamic cells targeted by cholinergic projections has been studied in more detail in nonauditory than in auditory nuclei. In general, cholinergic inputs target both thalamocortical cells and GABAergic interneurons as well as GABAergic neurons in the thalamic reticular nucleus. Depending on the thalamic nucleus, these inputs are positioned to modulate ascending sensory inputs to the thalamus or descending inputs from the cortex (e.g., Patel and Bickford 1997). Interestingly, there is also evidence for cholinergic inputs to the *axons* of medial geniculate thalamocortical cells (Kawai et al. 2007). These inputs activate nicotinic receptors at nodes on myelinated axons in the thalamic radiations, serving to increase the efficacy of transmission of sensory information to auditory cortex. This unusual mode of action represents a rarely recognized possibility for neuromodulation. It is likely that these cholinergic inputs originate from the PMT or the basal forebrain, but the sources have not been identified directly.

In addition to the projections to the thalamus, the PMT provides cholinergic input to the inferior colliculus and regions of the cochlear nucleus (reviewed in Schofield et al. 2011). The projections to each of these areas originate from more cells in the PPT than in the LDT, but each area receives projections from both cholinergic nuclei. The PMT is the predominant source of cholinergic projections to the inferior colliculus; however, recent studies have revealed a projection from the LPGi as well (Motts and Schofield 2009; Stornetta et al. 2013). Cholinergic fibers terminate throughout the inferior colliculus and a majority of collicular cells are affected by locally applied cholinergic agents. Thus far, GABAergic inferior collicular cells are the only ones identified as receiving direct cholinergic inputs (Yigit et al. 2003). The PMT projections to the cochlear nucleus are known to terminate in the dorsal cochlear nucleus (Mellott et al. 2011), but the specific cell types contacted and whether the PMT projects at all to the ventral cochlear nucleus are unknown.

The PMT is also a source of cholinergic projections to the caudal pontine reticular nucleus. While not a component of the ascending auditory system, the caudal pontine reticular nucleus is a critical premotor component of the startle circuit and is activated during the acoustic startle reflex. The cholinergic projection from the PMT to the caudal pontine reticular nucleus is critical for prepulse inhibition of acoustic startle (Bosch and Schmid 2008). Thus cholinergic projections from the PMT may allow for enhanced (or protected) sensory processing via projections to auditory nuclei while suppressing the motor component of a startle response via projections to premotor nuclei.

9.2.2.3 Cholinergic Cells in the Lateral Paragigantocellular Nucleus

The lateral paragigantocellular nucleus (LPGi) is a small nucleus of the reticular formation located just caudal to the facial nucleus and superior olivary complex and lateral to the pyramids; it is also called the rostral ventrolateral medulla (see discussion in Bellintani-Guardia et al. 1996). This nucleus has been associated with polymodal sensory integration, with the autonomic nervous system, and with control of cardiorespiratory function (Van Bockstaele et al. 1993). Stornetta et al. (2013) used chemically selective tracing techniques to demonstrate that the cholinergic cells in the LPGi project to numerous auditory nuclei but not to the autonomic and cardiorespiratory centers. These cholinergic projections terminate in the dorsal cochlear nucleus as well as parts of the superior olivary complex and inferior colliculus. The target cells in these areas are unknown. The LPGi receives input from several auditory nuclei (cochlear nucleus, inferior colliculus, auditory cortex), but the relationships of these inputs to the cholinergic cells are unknown.

9.2.2.4 Cholinergic Cells in the Superior Olivary Complex

The superior olivary complex is the origin of the most studied cholinergic projections in the auditory brainstem (Ryugo et al. 2011). Targets of these projections are primarily auditory structures (Brown 2011). The best known cholinergic projection from the superior olivary complex is the olivocochlear projection. The olivocochlear system consists of medial and lateral divisions that have different connections and different functions. Most of our knowledge about this system is associated with the medial olivocochlear system, which acts on outer hair cells to modulate cochlear function. Medial olivocochlear axons have collateral branches that terminate in the cochlear nucleus where the cholinergic inputs likely modulate the activity of stellate cells (Benson and Brown 1990; Oertel et al. 2011). Lateral olivocochlear cells terminate on primary afferent fibers associated with inner hair cells in the cochlea and presumably modulate input at the origin of the auditory pathway. These lateral olivocochlear cells may also have collateral projections to the cochlear nucleus but much less is known about them. The superior olivary complex also contains a group of cholinergic cells that innervate the cochlear nucleus, but they do not project to the cochlea (Sherriff and Henderson 1994). The targets of these nonolivocochlear projections appear to include the cochlear root neurons (Gómez-Nieto et al. 2008) and perhaps other parts of the ventral cochlear nucleus. The roles of these various inputs and the possibility that multiple inputs converge on the same cells in the cochlear nucleus have only begun to be explored.

9.2.3 Noradrenaline

Noradrenergic projections terminate in all auditory centers from the cochlear nucleus to the cortex. The details of termination patterns have been described for some areas, including auditory cortex (Levitt and Moore 1978; Campbell et al.

1987), cochlear nucleus and inferior colliculus (Klepper and Herbert 1991), and superior olivary complex (Mulders and Robertson 2001). In the auditory cortex, noradrenergic fibers terminate in all cortical layers with the densest termination in layer I (Levitt and Moore 1978; Campbell et al. 1987). There is a high degree of collateralization, suggesting that single fibers terminate on many target cells in multiple layers. Little is known about the specific cells targeted by noradrenergic inputs to auditory cortex.

Noradrenergic fibers terminate in multiple areas of the cochlear nucleus with only the granule cell area and the molecular layer of the dorsal cochlear nucleus singled out as receiving minimal noradrenergic innervation. Thus, there is ample opportunity for a majority of the cell types in the cochlear nucleus to receive noradrenergic input but, to date, only cochlear root neurons have been identified specifically as likely targets of noradrenergic axons (Gómez-Nieto et al. 2008). Noradrenaline also broadly innervates the superior olivary complex (Mulders and Robertson 2005a). The innervation density varies across nuclei and in some cases within nuclei, suggesting varying levels of noradrenergic effects on different olivary circuits. Thus far, noradrenergic inputs have been associated with olivocochlear cells (Mulders and Robertson 2000) and with olivary cells that project to the cochlear nucleus (Behrens et al. 2002). Finally, noradrenergic fibers terminate throughout the inferior colliculus, where the density of fibers varies both across and within subdivisions (Klepper and Herbert 1991). The same authors described noradrenergic fibers terminating throughout the nuclei of the lateral lemniscus, but they did not describe termination patterns in detail. In none of these areas (lemniscal nuclei or inferior colliculus) have the targets of the noradrenergic fibers been identified.

The major source of noradrenergic innervation is the locus coeruleus (Berridge and Waterhouse 2003). For some areas (e.g., auditory cortex), the locus coeruleus is the sole source of noradrenergic innervation, but other areas (e.g., cochlear nucleus) receive smaller contributions (depending on species) that originate in other nuclei of the reticular formation (Klepper and Herbert 1991).

9.2.4 Dopamine

Dopaminergic fibers or dopamine receptors have been described in the cochlea, cochlear nucleus, nuclei of the lateral lemniscus, inferior colliculus, and auditory cortex (Tong et al. 2005; Descarries and Mechawar 2008). Dopaminergic fibers are reportedly absent from the superior olivary complex (Mulders and Robertson 2005a).

Dopaminergic input to the cochlea is associated with lateral olivocochlear fibers that terminate on primary afferent fibers receiving input from inner hair cells (Mulders and Robertson 2004; Darrow et al. 2006). Studies suggest that the dopaminergic efferents inhibit responses in auditory nerve fibers and may provide some protection against acoustic trauma (Le Prell et al. 2005; Niu et al. 2007).

The sources of dopaminergic innervation for the rest of the auditory system are less clear. Dopaminergic projections to much of the central nervous system originate

in the ventral midbrain, including the substantia nigra and ventral tegmental area along with several adjacent areas (Yetnikoff et al. 2014). It is likely that these nuclei innervate auditory cortex and perhaps some subcortical auditory regions. In addition, there is evidence for dopaminergic cells within several auditory regions, including the inferior colliculus, nuclei of the lateral lemniscus, and as described previously, the superior olivary complex (Altschuler and Shore 2010). Other than the olivocochlear projections, the projections of dopaminergic cells located within auditory nuclei are unknown.

9.2.5 Serotonin

Serotonin neurons are located in a series of raphe nuclei that are distributed on or near the midline from the medulla to the midbrain (Descarries and Mechawar 2008). Nine nuclei are usually distinguished. Together, these nuclei project throughout much of the central nervous system, from spinal cord to neocortex. The nuclei have been divided into superior and inferior groups (Jacobs and Azmitia 1992). The *superior group* consists of the dorsal raphe, median raphe, and caudal linear nuclei, as well as group B9. The *inferior group* consists of nuclei raphe obscurus, raphe pallidus, and raphe magnus, as well as the LPGi and the area postrema. There is a rough topography such that the inferior group nuclei project to the medulla and spinal cord, whereas the superior nuclei project to the forebrain. More refined distinctions that could relate to functional differences might apply to projections from different cell groups within individual nuclei (Commons 2015).

As a group, the serotonergic nuclei appear to project to all auditory nuclei. Details of the origins of projections to the auditory cortex and auditory thalamus are limited; most of the information is available within broader studies not focused on the auditory system (Descarries and Mechawar 2008). The data suggest that the dorsal and median raphe nuclei, which are two of the largest serotonergic nuclei, provide the main innervation of auditory forebrain.

Origins of serotonin innervation of brainstem auditory nuclei have been studied in more detail. Serotonergic fibers terminate throughout the cochlear nucleus with the densest terminations in the molecular layer of the dorsal cochlear nucleus and the granule cell area. The inferior colliculus also receives serotonin inputs that terminate across all subdivisions but terminate most heavily in the dorsal and external cortex. The cochlear nucleus and the inferior colliculus receive predominant input from the dorsal raphe with small contributions from other raphe nuclei (Klepper and Herbert 1991). The smaller contributions originate mostly from the superior group but include some contributions from inferior group nuclei. One such nucleus is the LPGi, described previously for its contingent of cholinergic cells. Serotonergic cells in the LPGi project to the cochlear nuclei or the inferior colliculus and appear to receive direct inputs from the cochlear nucleus (Bellintani-Guardia et al. 1996). These inputs arise in part from cochlear root neurons, which could provide for rapid activation of the serotonergic cells by acoustic stimuli.

Serotonin fibers also innervate the nuclei of the lateral lemniscus and superior olivary complex (Klepper and Herbert 1991; Thompson and Hurley 2004). The sources of this innervation are assumed to be among the raphe nuclei, but they have yet to be identified directly. The terminations vary in density between different nuclei, and the patterns may also differ between species (Woods and Azeredo 1999; Hurley and Thompson 2001). The target cells in lemniscal nuclei are unknown. Serotonin-targeted cells in the superior olivary complex are likely to include cells that project to the cochlea or to the cochlear nucleus (Brown 2011).

9.2.6 Some Remaining Issues Regarding Modulatory Anatomy

Many questions remain to be addressed about the anatomical organization of modulatory inputs to auditory circuits. The previous discussions included relatively little detail on modulatory circuits in the auditory cortex. To a degree this reflects a common perspective that many circuits and actions are similar across cortical areas and thalamic nuclei (acknowledging, for example, a distinction between first- and higher-order nuclei in the thalamus) (Sherman and Guillery 2011; Varela 2014). Of the neuromodulators discussed in the present chapter, acetylcholine has been studied most extensively in auditory thalamus and cortex. Many additional insights for all four modulators might be gained by considering work in other systems. Studies in multiple cortical areas have emphasized modulatory effects on different subclasses of GABAergic interneurons (e.g., reviewed by Bacci et al. 2005).

Recent work supports the distinction of interneuron types in auditory cortex and suggests that the different types have distinct physiological characteristics (Li et al. 2015; Mesik et al. 2015). In several cortical areas a given modulator, such as noradrenaline, can excite or inhibit different types of interneurons. Because different interneuron types have different projection patterns within the cortex, a simple (i.e., relatively nonspecific) modulatory input can have dramatic effects on information flow within the cortex. Such effects are proposed to switch cortical processing between an intracolumnar versus a horizontal (i.e., transcolumnar) mode (Bacci et al. 2005). If such a process occurs in auditory cortex, one could predict modulation that, for example, could promote cross-frequency (horizontal) integration versus columnar processing that might promote frequency discrimination. An interesting possibility is that the different modulators take advantage of the same GABAergic circuitry to dynamically shift cortical processing strategies. Differences between the modulators, then, would depend primarily upon the different circumstances under which each modulatory system is active.

Highly collateralized projections have long been associated with modulatory systems whereby individual axons branch many times to innervate many different areas. To some extent such collateralization is implied by the widespread innervation of the central nervous system by a relatively small number of neurons. Numerous studies have identified widespread collaterals in serotonergic and noradrenergic systems (see discussions in Berridge and Waterhouse 2003; Descarries and

Mechawar 2008). The extent of collateral projections to auditory nuclei has not been studied extensively, but collateral projections are common in cholinergic innervation of the auditory brainstem (Schofield et al. 2011). However, there is evidence that broad collateralization is not universal among modulatory projections, such as in the quite limited collateral branching among dopaminergic projections (Descarries and Mechawar 2008). This means that the dopaminergic projections to different targets originate from separate groups of cells (that may or may not be intermingled). The key point is that branched axons can allow for broad actions but with limited opportunity for differential effects on targets, whereas innervation by separate sets of source neurons can facilitate distinct effects in different targets. Many questions remain about the degree of branching of modulatory projections to auditory targets.

Another issue related to breadth versus specificity of action is that of synaptic release versus volume transmission (discussed by Descarries and Mechawar 2008). Volume transmission implies slower onset and longer duration of action compared to synaptic transmission and often has been associated with modulatory circuits. The frequency with which axonal swellings form traditional synapses varies according to target area, modulator, and perhaps species. Furthermore, the assumption of volume transmission has often followed from an inability to identify synapses that include a traditional synaptic junction (with visible postsynaptic density). Recent work suggests that cholinergic synapses may include those with traditional densities as well as some without such densities (e.g., Takács et al. 2013). These nontraditional synapses can be associated with typical clusters of postsynaptic receptors and otherwise allow all the specificity associated with traditional synapses. Indeed, physiological studies argue that ACh can exert highly specific effects in neocortex (Muñoz and Rudy 2014).

9.3 Physiology and Function of Modulatory Circuits

9.3.1 Neuromodulatory Anatomy Provides a Blueprint for Function

The anatomical pathways connecting modulatory nuclei with their inputs provide a blueprint for understanding their function. Most centralized neuromodulatory systems receive projections from an impressive variety of brain regions. These range from primary sensory areas to more integrative neural centers that respond to sensory information as it is filtered by factors such as motivational state or top-down cognitive processing (e.g., Sarter et al. 2005; Yetnikoff et al. 2014). These inputs converge directly on neuromodulatory neurons or onto local interneurons, providing a substrate for the multifactorial control of spiking activity (Challis et al. 2013; Yetnikoff et al. 2014). These patterns of anatomical connection give rise to a model in which neuromodulatory centers receive information from many sources, sort and

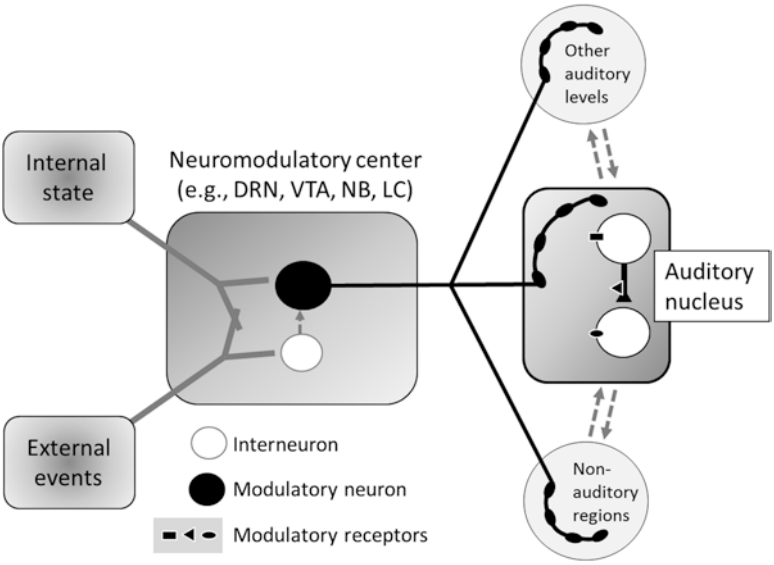

Fig. 9.1 Depiction of a model of neuromodulatory function, emphasizing the integration of information from diverse sources by neuromodulatory centers and its subsequent projection to multiple auditory and other brain regions. *DRN*, dorsal raphe nucleus; *LC*, locus coeruleus; *NB*, nucleus basalis; *VTA*, ventral tegmental area [Taken from Velho et al. (2012) with permission]

prioritize it, and then send it to multiple auditory destinations in the form of specific neurochemicals like dopamine and noradrenaline (both catecholamines), acetylcholine, and serotonin (Fig. 9.1). As a result of this process, neuromodulatory neurons are in a prime position to signal salient aspects of behavioral context to the auditory system.

The conveyance of salient information by neuromodulatory pathways is only half of the equation; auditory neurons must also interpret this information. This is accomplished through the expression of neuromodulatory receptors by auditory neurons themselves. This aspect of neuromodulatory function provides expansive opportunities for the regulation of excitatory and inhibitory circuitry in the auditory system through a diversity of receptor types (Edeline 2012; Hurley and Sullivan 2012). Receptor diversity allows even single neuromodulators to create sophisticated profiles of effects on auditory circuitry. In the partnership between neuromodulatory release and reception, local events at the level of auditory neurons can translate even broad-scale release into highly specific effects on auditory circuitry.

Although neuromodulatory systems clearly have a profound ability to organize auditory activity on both short- and long-term time scales, an integrated view of their function is very much a work in progress. Therefore, the following sections are organized into two major conceptual divisions. The first of these describes a functional "toolbox" highlighting some prominent features of neuromodulatory function in the auditory system. In some of these sections, work in the auditory systems of songbirds provided useful comparative models that emphasize neuromodulation as

it relates to the behavioral salience of natural vocal signals. The concepts developed in this section are then applied to speculation about a broad functional role for neuromodulatory systems with high relevance to auditory research: responses of the central auditory system to hearing loss.

9.3.2 A Toolbox of Neuromodulatory Function

9.3.2.1 How is Neuromodulatory Function Measured?

Auditory neuromodulation can be assessed at multiple points along the pathway from release to reception with different methods providing different types of information (Fig. 9.2). The specific sorts of events or states represented by neuromodulatory systems can be inferred from the electrophysiological or transcriptional responses of central neuromodulatory neurons to different types of behavioral events (Fig. 9.2A) (Bharati and Goodson 2006; Gale and Perkel 2010). Variation in neuromodulatory activity within auditory regions can be captured by comparing the levels of neuromodulators and their products in dissected tissues as indicative of *turnover* (a measure of release and subsequent metabolism) (Cransac et al. 1998). Time courses of neuromodulatory activity can be tracked with repeated measurements in behaving animals with microdialysis followed by neurochemical analysis or by electrochemically forcing neuromodulatory oxidation and measuring the corresponding currents with carbon fiber voltammetry (Fig. 9.2B) (Stark and Scheich 1997; Hall et al. 2010).

On the postsynaptic side, responses of auditory neurons to neuromodulators are often presented as changes in spontaneous or evoked spike rate or timing during application of neuromodulatory agonists or antagonists or during stimulation of neuromodulatory centers (Fig. 9.2C) (Edeline et al. 2011; Salgado et al. 2011). Finally, plasticity in modulatory input to auditory regions can be represented by increases or decreases in the density of projections immunolabeled for neuromodulatory synthetic enzymes or selective transporters (Matragrano et al. 2012a; Papesh and Hurley 2012). These different types of measurements contribute to a portrait of relevant neuromodulatory events occurring on multiple timescales with short-term changes in response to behaviorally salient events superimposed on longer state-dependent or experience-dependent fluctuations.

9.3.2.2 Neuromodulators are Sensitive to Behavioral Context: Internal State and Salient Events

Modeling the neuromodulatory regulation of auditory circuitry requires an understanding of the behavioral conditions evoking neuromodulatory release. Neuromodulatory pathways operating within the auditory system are responsive to many of the factors that define behavioral context, including the nature of external

Fig. 9.2 Illustration of methods for measuring neuromodulatory function. **(A)** Co-label of synthetic enzyme for catecholamines (*green*) with a marker of immediate early gene expression (*red*). *Arrows* and *asterisk* indicate double-labeled neurons; *scale bar:* 100 μm. **(B)** Increase in electrochemically measured serotonin in the inferior colliculus during physical restriction. **(C)** Example of modulatory effects on a spike train in response to a vocalization playback. *Top*: oscillogram and spectrogram of a mouse vocalization. *Middle*: Raster plot of the response of a single inferior colliculus neuron to the call in the top panel (*control*). *Bottom panel*: Response of the same neuron to the same call during agonism of serotonin receptors (*modulated*). (*A8*, *A11*, aminergic cell groups; *CA*, cerebral aqueduct; *CG*, central gray of the midbrain) [**A** from Bharati and Goodson (2006), used with permission; **B** adapted from Hall et al. (2012); **C** unpublished data from L. Hurley]

events, internal state, and past experience (Cransac et al. 1998; Hurley and Hall 2011). Neuromodulators are often described as broadly mediating the effects of behavioral arousal or attention but also convey nuanced information on variation within behavioral contexts.

Neurons at many levels of the auditory system respond differently during different phases of the sleep-wake cycle (Velluti 2008). All of the neuromodulatory systems described in this chapter also show activity that is tied to the sleep-wake cycle. Higher levels of firing or different firing modes by neuromodulatory neurons, coupled with greater release of neuromodulators in target areas, typically correspond to waking states but also vary across different phases of the sleep-wake cycle (NA: Berridge and Waterhouse 2003; ACh: Lee et al. 2005; DA: Monti and Monti 2007). Although comparisons of neuromodulatory activity between sleep and waking have been made rarely within the auditory system, the effects of neuromodulators administered to auditory regions may qualitatively or quantitatively depend on the level of arousal (Manunta and Edeline 1999; Cardin and Schmidt 2004). In a similar vein, the levels of at least one neuromodulator, serotonin, rise in the auditory midbrain of mice during recovery from anesthesia, as a relationship to general arousal would predict (Hall et al. 2010).

Neuromodulators in the auditory system respond to behaviorally salient events, from imposed stressors to interaction with conspecifics, a class of behavioral events with special relevance to vocal communication. External stressors quickly increase the activity of multiple neuromodulators in different auditory areas. Serotonin rap-

idly and robustly increases in level during spatial confinement (Fig. 9.2B), and serotonin and noradrenaline both show increased turnover in some brainstem or midbrain regions in response to increasing levels of noise exposure (Cransac et al. 1998; Hall et al. 2012). Studies in multiple vertebrate species have demonstrated that auditory neuromodulators are also highly responsive to the signals of social partners. In the auditory midbrain of male and female mice, increases in serotonin occur during interaction with a partner of the opposite or same sex (Fig. 9.3A) (Hall et al. 2011; Hanson and Hurley 2014). Vocal signals alone are sufficient to trigger changes in catecholaminergic activity in auditory forebrain regions in some songbirds (Matragrano et al. 2012a). Catecholaminergic neurons themselves respond to species-specific vocal signals (Petersen et al. 2013), and in songbirds, dopaminergic neurons can also show selective responses to an individual's own song, a highly salient stimulus for song learning (Gale and Perkel 2010). Remarkably, neuromodulatory activity may even be selective for behaviorally salient variation within social contexts. Songbirds exposed to more challenging songs of rivals or to "sexier" songs of potential mates have higher levels of catecholaminergic activity in auditory forebrain areas than those exposed to less challenging or less attractive songs (Sockman and Salvante 2008; Sewall et al. 2013. Likewise, elevated serotonin in the inferior colliculus of mice correlates with increased social investigation (Hall et al. 2010).

If a single broad function can be ascribed to neuromodulators in auditory processing, it is that they alter the representation of acoustic stimuli in accordance with salient events, but different neuromodulatory pathways are often described in distinct functional terms. Serotonin has been linked to negative salience and stress as well as to social behavior (Dayan and Huys 2008; Kiser et al. 2012). Acetylcholine has been linked to cue-directed attention and focus (Sarter et al. 2014). Noradrenaline has been linked to arousal and stimulus-directed cognitive shifts (Berridge and Waterhouse 2003; Bouret and Sara 2005) and dopamine has been linked to reward contingencies (Chandler et al. 2014; Pignatelli and Bonci 2015). However, comparison of neuromodulatory responses in the same behavioral paradigms depicts activity in different pathways that, while distinct in some regards, is overlapping in others (Bouret and Sara 2005; Chandler et al. 2014). For instance, multiple neuromodulators represent the behavioral certainty of sensory cues in predicting subsequent events (Sarter et al. 2014; Pignatelli and Bonci 2015). Within the auditory system itself, an example of neuromodulatory overlap is seen in an increase in both serotonergic and dopaminergic metabolites in auditory cortex during associative training sessions (Stark and Scheich 1997). This dual increase was potentially indicative of general stress. However, the dopaminergic metabolite, unlike the serotonergic metabolite, increased most during an initial session for animals that were presented with tones that were predictive of shock, paralleling conditioned behavior. Thus, activity of different neuromodulatory pathways in the auditory system may reflect each other during some behavioral circumstances, but diverge during others in relation to specific behaviors.

In summary, although direct measurement has been rare, neuromodulatory activity within the auditory system is broadly linked to behavioral arousal, and neuro-

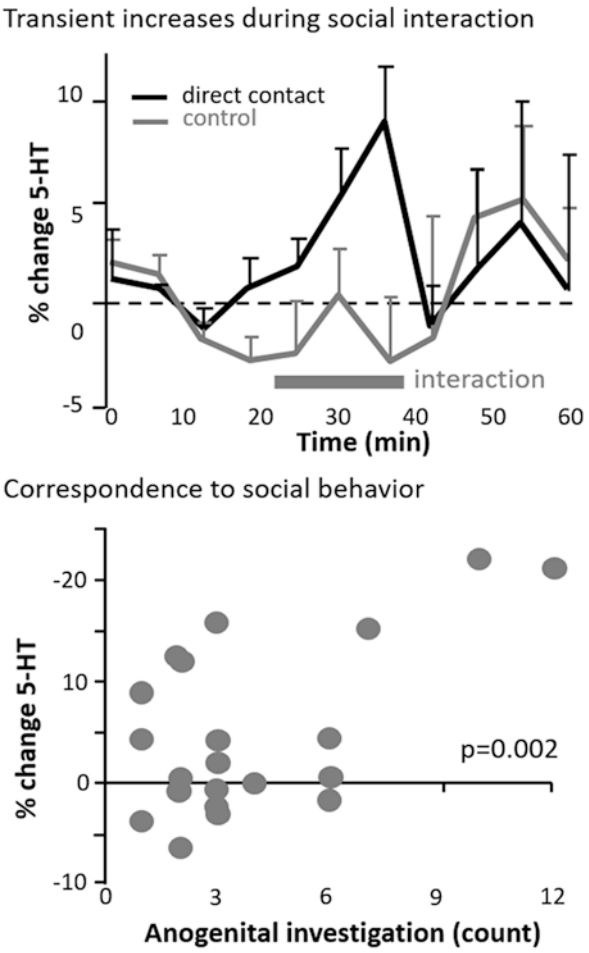

Fig. 9.3 Neuromodulatory activity and effects are related to social context. Serotonin levels (*top*) increase during a social interaction; individual variation in serotonergic change correlates with individual variation in social behavior (*bottom*). P-value taken from multivariate regression. [Modified from Hall et al. (2011)]

modulators also encode information on variation within behavioral contexts like social interaction and associative training. Rather than being entirely separate in functional domains, it is likely that profiles of different neuromodulators signal behaviorally salient events.

9.3.2.3 Neuromodulators Functionally Reconfigure Auditory Circuitry

Approaches to studying the short-term effects of neuromodulators on ongoing auditory processing have included studies in vivo or in brain slice preparations during presentation of sound or electrical stimulation of input pathways and accompanied by stimulation of neuromodulatory centers or application of exogenous agonists and antagonists. Despite this wide range of approaches, most neuromodulatory effects

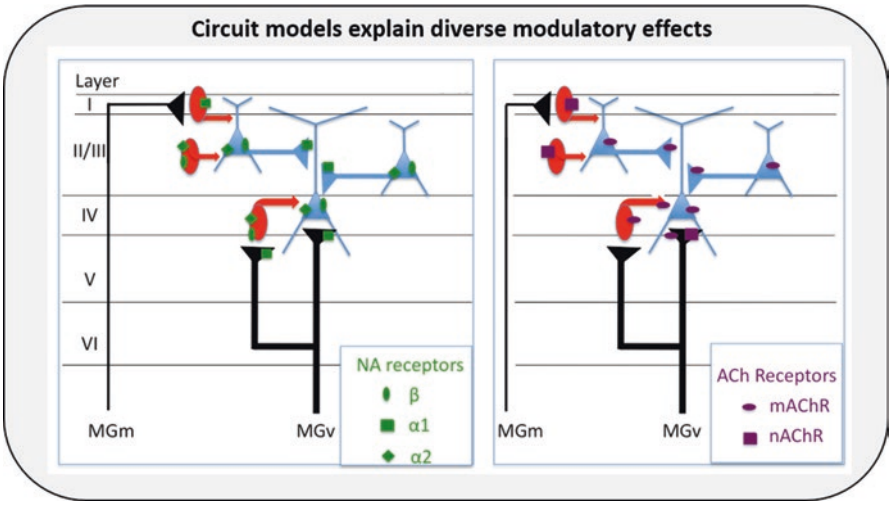

Fig. 9.4 Conceptual representation of neuromodulatory effects in auditory cortex as circuit reconfigurations, emphasizing intracortical versus thalamocortical processing. *Red ovals* and *arrows* represent inhibitory GABAergic interneurons, and *blue triangles and lines* represent glutamatergic neurons. (ACh, acetylcholine; MGm, medial geniculate body, medial subdivision; MGv, medial geniculate body, ventral subdivision; NA, noradrenaline. [From Edeline (2012) courtesy of the author]

in the auditory system are highly compatible with classic models of neuromodulatory function that originate in studies of invertebrate motor circuitry (Marder and Bucher 2007; Harris-Warrick and Johnson 2010). Given a complex neural circuit integrating inputs from multiple sources, these models portray neuromodulators as reconfiguring the flow of information by changing intrinsic properties and synaptic strengths (Fig. 9.4). What this confers on auditory circuitry is the flexibility to favor the configuration most appropriate to the circumstances triggering neuromodulatory release.

Reconfiguration of auditory circuits by neuromodulators occurs at multiple levels of auditory processing. In auditory cortex, several types of neuromodulators alter the balance between thalamocortical and intracortical processing. For example, a cholinergic agonist acting through muscarinic receptors dampens evoked polysynaptic inputs to cortical layer IV neurons and has less of a dampening effect on thalamocortically evoked fast potentials than on intracortically evoked fast potentials. Overall, this combination of effects promotes fast feedthrough processing (Hsieh et al. 2000). In contrast, dopamine acting through D1/D5 receptors prolongs input to the cortex by recruitment of a feedback loop through auditory thalamus, ultimately prolonging horizontal interactions within auditory cortex (Happel et al. 2014). Circuit reconfiguration is also seen at subcortical levels. In the dorsal cochlear nucleus, muscarinic acetylcholine receptors strengthen activity along a polysensory neural pathway by targeting multiple neuron types (fusiform cells: Chen et al. 1998; granule cells: Kőszeghy et al. 2012; cartwheel cells: He et al.

2014). Likewise, by influencing both principal neurons and inhibitory interneurons, serotonin increases the relative weight of polysensory inputs versus auditory inputs (Tang and Trussell 2017).

Acetylcholine, originating in projections from the ventral nucleus of the trapezoid body, also influences sources of auditory input to the cochlear nucleus, dampening cochlear amplification but increasing the responsiveness of T stellate neurons (Fujino and Oertel 2001). This constellation of effects could potentially influence the balance between auditory and polysensory information at the level of projection neurons from the cochlear nucleus (see Trussell and Oertel, Chap. 4).

Effects of dopamine, serotonin, noradrenaline, or acetylcholine have also been variously reported within many nuclei in the ascending auditory system, including the cochlear nucleus (Ebert and Ostwald 1992; Felix et al. 2017), medial nucleus of the trapezoid body (Leão and Von Gersdorff 2002), lateral superior olive (Fitzgerald and Sanes 1999), inferior colliculus (Fig. 9.4A) (Habbicht and Vater 1996; Hurley and Sullivan 2012; Gittelman et al. 2013), and medial geniculate body (Pape and McCormick 1989). Although most of these studies have examined the effects of single neuromodulators at unitary sites in the auditory system, there are two important points to be addressed in establishing the ultimate effects of neuromodulatory release. First, neuromodulators simultaneously acting at multiple auditory sites likely interact (Ma and Suga 2005), although this is a topic that in general has not been well-explored. Second, different neuromodulators commonly converge in their effects on single neuron types, a phenomenon that is exemplified by the effects of dopamine (Bender et al. 2010), acetylcholine (He et al. 2014), and noradrenaline (Kuo and Trussell 2011) on inhibitory cartwheel interneurons in the dorsal cochlear nucleus, but the phenomenon is seen at many sites along the auditory neuraxis. These findings suggest that different neuromodulatory systems do indeed have some of the same auditory targets and may interact in creative ways in line with overlaps in their release patterns.

Precisely how neuromodulators reconfigure particular auditory circuits depends on a range of factors, including which subtype of neuromodulatory receptor is activated, since different receptor types act via different intracellular effectors, ultimately influencing membrane properties in distinct ways (e.g., Ramos and Arnsten 2007; Hannon and Hoyer 2008). If particular receptor types are expressed by excitatory versus inhibitory neurons or in specific subcellular locations, the differences can lead to highly targeted effects on neural circuits and microcircuits. As convincing examples, dopamine modulates calcium influx through T-type channels found exclusively on the axon initial segment (but not on dendrites) of inhibitory cartwheel neurons of the dorsal cochlear nucleus (Bender et al. 2010), and serotonin acting through 5-HT1A receptors alters spike threshold in the axon initial segment of neurons in the medial superior olive (Ko et al. 2016). This results in a selective reduction of the spiking output of these neurons. Receptor type and location may also interact, as occurs for the effects of noradrenaline on the responses of layer II/III pyramidal neurons in auditory cortex (Salgado et al. 2011). Noradrenaline increases the amplitudes of inhibitory currents generated by stimulation of layer II/III inputs via α2 and β adrenergic receptors, but noradrenaline decreases inhibitory

currents generated by stimulation of layer I inputs via α1 receptors. The suggested result is an emphasis on the processing of nontonotopic or intracortical inputs.

An emergent property of this wide variety of receptor mechanisms is that neuromodulators often have effects that depend on the spectrotemporal structures of the auditory stimuli presented, extending to different effects on varied species-specific vocalizations (Hurley and Pollak 2005). Such stimulus dependence may be tied to behavioral salience, since manipulating modulatory systems, like the noradrenergic system, influences the ability of auditory neurons to encode relevant stimuli such as vocal signals (Fig. 9.5) (Castelino and Schmidt 2010; Ikeda et al. 2015). Stimulus dependence of neuromodulators fits well with the understanding of the mechanisms described above. Variation along a given stimulus dimension may create variation in the profiles of inputs, which are differentially sensitive to neuromodulation via specific types of receptors. However, this phenomenon raises concerns for interpreting neuromodulatory function in response to natural stimuli based on simpler stimuli like tones, since the two may be very different (Gaucher and Edeline 2015).

In summary, the effects of neuromodulators on auditory processing are prevalent and strong. Even single neuromodulators can reconfigure auditory circuitry through multiple receptor types and in multiple auditory regions, and multiple neuromodulators may converge at the level of single neuron types. This makes the effects of neuromodulators complex but confers the ability to produce a range of behaviorally appropriate outputs from auditory circuitry.

9.3.2.4 Neuromodulators Facilitate Long-Term Plasticity in Adults

Facilitating experience-dependent plasticity in the adult auditory system is a core part of the neuromodulatory portfolio. Within the auditory cortex, a paradigm that has been extensively explored is the facilitation of changes in frequency responsiveness following associative pairing of tones with aversive stimuli. This topic has been reviewed repeatedly from multiple perspectives (e.g., Froemke and Martins 2011; Weinberger 2015), so this subject is only briefly sampled here with special emphasis on the additional aspects of neuromodulatory function detailed in this chapter.

In the associative paradigm, changes in the receptive fields of auditory neurons can be produced by pairing an auditory stimulus with an unconditioned stimulus, like a brief shock, that confers predictive value on the tone (Bakin and Weinberger 1990; Weinberger 2007). Receptive field changes at the level of single neurons produce reorganization of the cortical tonotopic map, such that more neurons are more closely matched with the frequency of the conditioned stimulus (Fig. 9.6A) (Kilgard and Merzenich 1998) in a way that predicts individual variation in behavior (Bieszczad et al. 2013).

Acetylcholine plays an important role in this process. The release of acetylcholine within the auditory cortex tracks conditioning in that increased levels occur following tone–reward pairing, but not control treatment (Butt et al. 2009). Notably, phasic stimulation of the nucleus basalis, a major source of cholinergic input to auditory cortex (Bajo et al. 2014), can substitute for an unconditioned stimulus, so

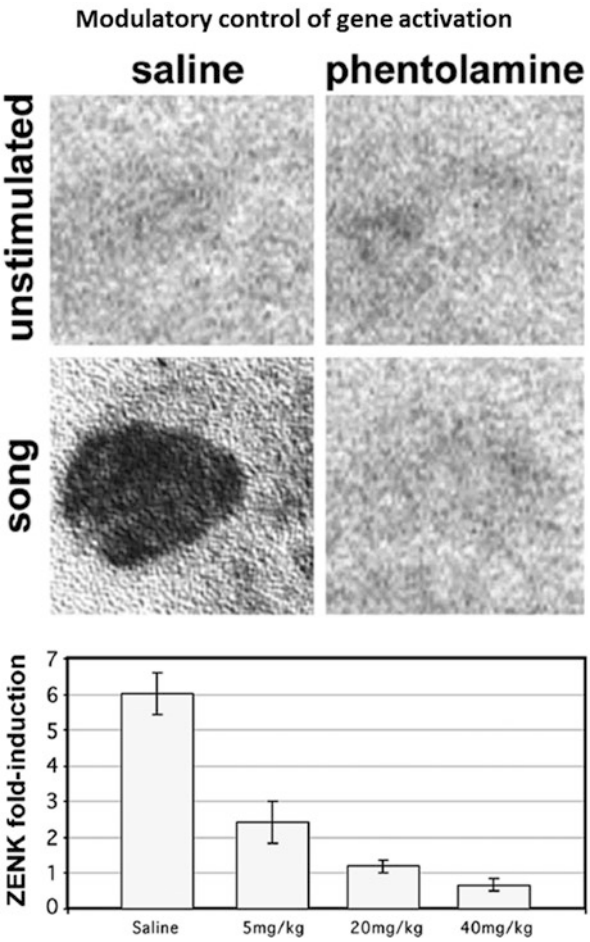

Fig. 9.5 Norepinephrine gates song-triggered gene activation in songbird auditory forebrain. *Top*: Blocking alpha adrenergic receptors with systemically administered phentolamine prevents playback of conspecific song from activating *zenk* transcription in auditory forebrain. *Bottom*: Dose-response relationship for the effects of phentolamine relative to saline injection (as control, shown in both). [Taken from Velho et al. (2012) with permission]

that paired but not unpaired stimulation shifts the best frequencies of many neurons closer to the frequency of the conditioned tone (Bakin and Weinberger 1996; Kilgard and Merzenich 1998). Finally, blocking endogenous sources of acetylcholine from activating muscarinic receptors can prevent many features of the associative changes in frequency tuning (Froemke et al. 2013). A characteristic that this process shares with short-term modulatory plasticity is that facilitation of shifts in tuning by acetylcholine relies on reconfiguration of cortical circuitry. At the level of synaptic inputs that underlie receptive field changes, pairing of a tone with stimulation of nucleus basalis initially causes a reduction of inhibition at the conditioned frequency that is followed by a re-balancing of excitation and inhibition to center around the new best frequency (Froemke and Martins 2011).

Neuromodulators other than acetylcholine also facilitate long-term changes in frequency tuning (Weinberger 2015). Direct application of serotonin or stimulating noradrenergic input causes changes in frequency tuning at the level of single corti-

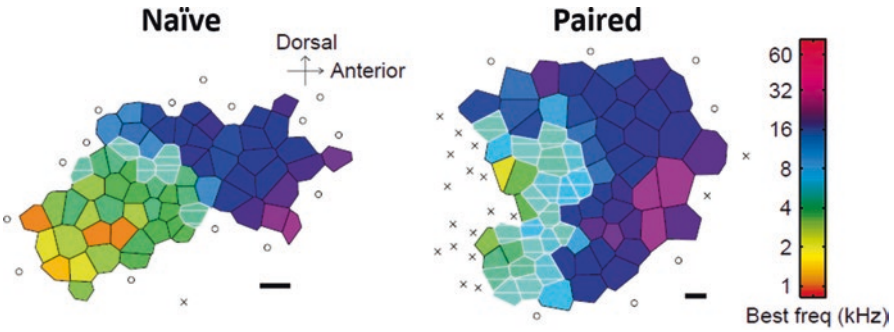

Fig. 9.6 Tonotopic reconfiguration in auditory cortex following pairing of tone presentation with neuromodulatory activation. A 9 kHz tone was paired with stimulation of the cholinergic nucleus basalis. *Light blue polygons* represent regions responding best to the conditioning frequency. *O* and *X* symbols represent sites that did not respond to tones or did not meet criterion values. (*Scale bar:* 200 μm) [Reprinted from Kilgard and Merzenich (1998) with permission from AAAS]

cal neurons, although these may occur in the opposite direction to those facilitated by acetylcholine (Ji and Suga 2007; Edeline et al. 2011). Dopamine also triggers plasticity in frequency tuning. In addition to dopaminergic activity in auditory cortex that occurs in parallel to behavioral conditioning (Stark and Scheich 1997), paired stimulation of the dopaminergic ventral tegmental area with tones produces a cortical remodeling emphasizing the representation of the conditioned frequency (Bao et al. 2001). Based on these studies, different neuromodulatory pathways may underlie associative representational plasticity in the auditory cortex.

Neuromodulators also are crucial to the expression of experience-dependent plasticity during natural communication behavior as illustrated by studies of noradrenaline and dopamine in songbirds. Blockage of noradrenergic receptors or chemical lesion of the noradrenergic system alters the presence or selectivity of transcriptional responses to the playback of song in the auditory forebrain (Lynch and Ball 2008; Velho et al. 2012). An interesting difference of the birdsong paradigm to the associative paradigm in mammals is that the neuromodulatory signal for salience in songbirds is in part triggered by the social stimulus of song itself. This is demonstrated by the responsiveness and selectivity of neuromodulatory neurons to species-specific acoustic signals (Gale and Perkel 2010; Petersen et al. 2013). These types of findings suggest that natural auditory stimuli have intrinsic salience within the context of social behavior that can be further enhanced by factors such as experience or reproductive state (Maney 2013). Such complexity may be typical of the relationships of stimuli to positive or negative salience in the natural world and can inform a view of neuromodulatory function as occurring through mutual instruction with primary sensory systems rather than as a unidirectional relationship.

In summary, neuromodulators help to cement the functional reconfiguration of auditory circuits into lasting changes in stimulus coding. These changes adapt auditory responses in the long term to emphasize stimuli that have occurred during behaviorally salient events like aversive episodes or social interaction.

9.3.2.5 Neuromodulatory Systems are Plastic

In addition to facilitating short- and long-term plasticity in auditory circuits, the portions of neuromodulatory systems localized within auditory regions themselves show a high degree of plasticity in response to changes in both physiological state and peripheral input. This is seen at virtually every level of organization important to modulatory function: in the innervation of auditory regions, the release of neuromodulators, and the expression of receptors. Factors that trigger such plasticity include reproductive state as signaled by gonadal hormones. Priming female songbirds with estradiol increases the density of catecholaminergic and serotonergic fibers, as well as the levels of noradrenaline and of a serotonergic metabolite in the auditory forebrain or midbrain (Matragrano et al. 2011, 2012b). Hearing loss has a significant impact on neuromodulatory projections (Papesh and Hurley 2012), ligand receptor binding (Jin et al. 2006), and receptor expression (Holt et al. 2005; Smith et al. 2014). More subtle changes in peripheral input, such as the makeup of the social environment, can also trigger neuromodulatory plasticity (Sockman and Salvante 2008; Sewall et al. 2013). These types of plasticity allow adaptation of neuromodulatory systems to changes in the average stimulus environment or internal state.

9.3.3 Neuromodulators Help Organize Auditory Responses to Noise and Social Contexts

The wide range of neuromodulatory effects described in an earlier section reflects the aims and approaches of divergent domains of auditory research. In some ways, this diversity makes it difficult to formulate integrated views of the roles of neuromodulators in auditory function. The aim of the following section, therefore, is to gather information on neuromodulation from a spectrum of studies addressing an active area of auditory research: exposure to noise and subsequent hearing loss. Neuromodulatory systems are sensitive to many of the factors related to hearing loss and its related outcomes, including exposure to noise and stress (Knipper et al. 2013). Therefore, it is not especially surprising that many features of neuromodulatory function are consistent with a model of these systems contributing to the central auditory response to noise exposure and hearing loss.

9.3.3.1 Exposure to Noise Recruits Neuromodulatory Systems

Neuromodulators could play a role in the very earliest responses of the auditory system to noise exposure. Increased transcriptional activity by modulatory neurons themselves during exposure to noise, a paradigm for inducing stress, occurs in multiple modulatory systems (Campeau and Watson 1997). Measurements along the

auditory neuraxis confirm that neuromodulatory activity responds to noise. Serotonin levels increase rapidly and remain elevated in the inferior colliculus in response to moderate noise levels (Hall et al. 2012). Serotonergic and noradrenergic turnover are also influenced by the presentation of noise, although this may vary among regions or stimulus intensities (Cransac et al. 1998). These findings suggest that, in general, neuromodulators are recruited by noise, but this recruitment may vary across auditory regions or with stimulus characteristics.

9.3.3.2 Olivocochlear Pathways Under Strong Neuromodulatory Control

Because one proposed role for medial olivocochlear projections is to protect cochlear function during exposure to potentially damaging noise (Maison and Liberman 2000; Le Prell et al. 2003), it is interesting that retrogradely labeled olivocochlear neurons are in close proximity to both noradrenergic fibers (Woods and Azeredo 1999; Mulders and Robertson 2000) and serotonergic fibers (Thompson and Thompson 1995; Woods and Azeredo 1999). Moreover, the application of either noradrenaline or serotonin has predominantly excitatory effects on neurons in this region (Wang and Robertson 1997), suggesting that neuromodulation could contribute to dampening cochlear output. Indeed, injecting noradrenaline in the vicinity of medial olivocochlear neurons decreases the amplitude of the compound action potential (Mulders and Robertson 2005b). Taken together, these studies suggest that central noradrenaline or serotonin could facilitate efferent control of cochlear responsiveness. This phenomenon could result in the facilitation of either protection from noise or of additional proposed functions of the medial olivocochlear pathway, such as improving the processing of signals in noise (Elgoyhen and Katz 2012).

9.3.3.3 Auditory and Neuromodulatory Circuitry Changes After Hearing Loss

An important model for the response of the central auditory system to cochlear damage proposes that a reduction in peripheral input triggers changes in the balance between excitation and inhibition, leading to compensatory central hyperactivity or altered tonotopic interactions (Salvi et al. 2000; Eggermont 2003). These types of changes may create auditory processing that is dysfunctional in level or timing, or they may lead to perceptual abnormalities like tinnitus and hyperacusis (Møller 2007; Noreña 2011). To the extent that neuromodulatory systems regulate excitatory/inhibitory balance, they could interact with these processes. This is exemplified by the serotonergic system, which has long been noted to dampen auditory gain (Hegerl et al. 2001; O'Neill et al. 2008) and has been linked to inhibition or suppression at the level of single neurons (DeFelipe et al. 1991; Wang et al. 2008). Another feature of the serotonergic system, which has lent itself especially well to hypotheses on central auditory plasticity, is its own sensitivity to hearing loss. Acoustic trauma alters the density of serotonergic projections to the inferior colliculus

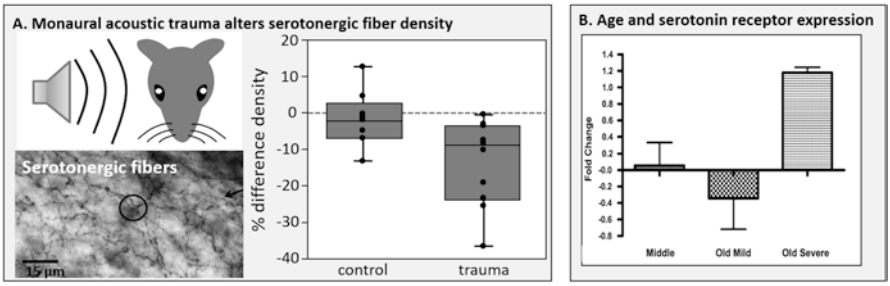

Fig. 9.7 Hearing loss influences the serotonergic system. **(A)** Monaural acoustic trauma decreases the ratio of projections in the contralateral versus ipsilateral inferior colliculus (interaction of side _ treatment, $F_{(1,16)} = 5.90$, Bonferroni post-hoc test $p < 0.05$). Circle in photomicrograph represents "spaceball" sampling technique used to stereologically estimate fiber density. **(B)** In old mice with severe hearing loss, expression of the 5-HT2B receptor is increased. *Middle,* middle-aged mice with good hearing; *Old mild*, old mice with mild hearing loss; *Old severe*, old mice with severe hearing loss. [**A** adapted from Papesh and Hurley (2012); **B** reprinted from Tadros et al. (2007) with permission from Elsevier]

(Fig. 9.7A) (Papesh and Hurley 2012). Multiple independent studies have further documented the upregulation or downregulation of serotonin receptor expression in the same region following hearing loss caused by acoustic trauma (Smith et al. 2014), or cochlear ablation (Holt et al. 2005), or in correspondence with aging (Fig. 9.7B) (Tadros et al. 2007). In a study directly comparing multiple types of serotonin receptors, the 5-HT1B receptor, a type that putatively decreases GABAergic input to inferior colliculus neurons, showed heightened upregulation in response to manipulations, including acoustic trauma (Hurley et al. 2008; Smith et al. 2014). Whether these changes in expression correspond to greater serotonergic control of inhibitory circuitry following hearing loss has not been investigated.

9.3.3.4 Neuromodulators and Auditory Dysfunction Following Hearing Loss

The direct evidence for a link between neuromodulators like serotonin and hearing loss-related disorders, such as tinnitus, is decidedly mixed. Selective serotonin reuptake inhibitors can influence the perception of tinnitus positively, negatively, or not at all, and often in correspondence with the symptoms of depression (Robinson et al. 2007; Baldo et al. 2012). A supporting link between serotonin and tinnitus is provided by salicylate, a drug that produces temporary tinnitus. Acute salicylate injection causes increased immunostaining of immediate early gene products in serotonergic cell groups (Caperton and Thompson 2011) and increases the activity of serotonergic raphe neurons by suppressing inhibitory inputs (Jin et al. 2015). In the inferior colliculus, salicylate triggers a substantial increase in serotonin (Liu et al. 2003) and also diminishes the ability of 5-HT2A receptors to enhance inhibitory postsynaptic currents (Wang et al. 2008). Paths forward through these diverse

sets of evidence may be increasing the specificity of experimental approaches by targeting particular receptor types, as well as by quantifying sources of individual variability, such as polymorphisms, in neuromodulatory machinery (Deniz et al. 2010).

In summary, diverse evidence supports a family of hypotheses on the involvement of neuromodulatory systems in both short- and long-term responses of the central auditory system to challenges by environmental noises. At this point, few of these broad hypotheses have been extensively tested, so they remain highly speculative, but they represent potentially fruitful areas for future exploration.

9.4 Summary and Challenges for the Future

Neuromodulators include a variety of signaling molecules and are a part of neural circuits at all levels of the auditory system. The modulators discussed here innervate auditory structures from cochlea to cortex. While much of the innervation arises from modulatory nuclei in the basal forebrain and brainstem, additional projections originate from neurons within auditory nuclei. Together, these modulators play a role in many functions and affect hearing according to internal state, behavioral arousal, and stimulus salience. Mechanisms of modulation are multiple and include the dynamic reconfiguration of circuits that often occurs at multiple levels of the auditory system. Finally, neuromodulators facilitate long-term plasticity. Such plasticity can underlie adaptive changes and may also be implicated in changes, including maladaptive ones, associated with hearing loss or other challenges to the system.

To better characterize circuits (the focal point of this book), it will be essential to identify the relationships between specific cell types in each auditory area and inputs from each modulatory system. Currently, these relationships are largely uncharacterized for the majority of auditory regions. Of course, where multiple sources of a modulator converge on a single target (e.g., for cholinergic inputs to the cochlear nucleus) the source must be related to each target cell type as well. Finally, synapses and receptors must be characterized and related to the physiological effects to understand modulation at a cellular level. To extend this understanding to a systems level, it will be necessary to understand the conditions under which each modulatory system is active and how those inputs affect circuit dynamics and information processing, as well as how these effects in different auditory regions interact with each other. Such information will lead to a more complete understanding of neural modulation of auditory perception and behavior.

Another area where information is incomplete concerns interactions between neuromodulatory cells in different nuclei or even within a single nucleus. For example, cholinergic cells in the PMT project to dopaminergic cells in the ventral tegmental area (Hong and Hikosaka 2014). The LPGi contains cholinergic, serotonergic, and adrenergic cells, each of which has ties to auditory circuits (Van Bockstaele et al. 1993; Bellintani-Guardia et al. 1996). In addition, the LPGi provides a major

input to the locus coeruleus, the main source of noradrenergic projections (Luppi et al. 1995). Understanding the interactions between the nuclei will have to be integrated with information on how different modulatory inputs converge on individual cells in auditory nuclei.

As a final reflection, although this chapter has focused on auditory effects of major neuromodulatory pathways, the diffuse projections from neuromodulatory cell groups indicate a broader role in coordinating activity across many neural systems to produce context-appropriate outputs. Ultimately, auditory-driven behaviors are likely to be influenced by parallel neuromodulatory effects on the auditory system and motor or affective systems. Equally broad effects of neuromodulators are likely to be seen during development. The most complete understanding of the influence of neuromodulation on auditory perception may best be achieved by considering these more global interactions.

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Laura Hurley declares that she has no conflict of interest.

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