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Cholinergic Cells of the Pontomesencephalic Tegmentum: Connections with Auditory Structures from Cochlear Nucleus to Cortex

Brett R. Schofield^{1,2}, Susan D. Motts^{1,2}, and Jeffrey G. Mellott, PhD¹

Susan D. Motts: smotts@neucom.edu; Jeffrey G. Mellott: jmellott@neucom.edu

¹ Department of Anatomy and Neurobiology, Northeastern Ohio Universities College of Medicine, Rootstown, OH 44272 USA

² School of Biomedical Sciences, Kent State University, Kent, OH, USA

Abstract

Acetylcholine (ACh) is a neuromodulator that is likely to play a role in plasticity as well as other phenomena at many sites in the auditory system. The auditory cortex receives cholinergic innervation from the basal forebrain, whereas the cochlea receives cholinergic innervation from the superior olivary complex. Much of the remainder of the auditory pathways receives innervation from the pedunculopontine and laterodorsal tegmental nuclei, two nuclei referred to collectively as the pontomesencephalic tegmentum (PMT). The PMT provides the major source of ACh to the auditory thalamus and the midbrain, and is a substantial source (in addition to the superior olivary complex) of ACh in the cochlear nucleus. Individual cholinergic cells in the PMT often have axon branches that innervate multiple auditory nuclei, including nuclei on both sides of the brain as well as nuclei at multiple levels of the auditory system. The auditory cortex has direct axonal projections to the PMT cells, including cholinergic cells that project to the inferior colliculus or cochlear nucleus. The divergent projections of PMT cholinergic cells suggest widespread effects on the auditory pathways. These effects are likely to include plasticity as well as novelty detection, sensory gating, reward behavior, arousal and attention. Descending projections from the forebrain, including the auditory cortex, are likely to provide a high level of cognitive input to these cholinergic effects. Dysfunction associated with the cholinergic system may play a role in disorders such as tinnitus and schizophrenia.

Keywords

inferior colliculus; tinnitus; plasticity; pedunculopontine tegmental nucleus; laterodorsal tegmental nucleus

1. Introduction

Acetylcholine (ACh) has effects at many sites within the auditory system. It has been studied in greatest detail at the two “ends” of the system: in the cochlea and the cortex. At

Correspondence: Brett R. Schofield, PhD, NEOUCOM, Department of Anatomy and Neurobiology, PO Box 95, Rootstown, OH 44272 USA, tel.: 330-325-6655, fax: 330-325-5916, bschofie@neucom.edu.

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the lower end, ACh is the primary neurotransmitter in most olivocochlear cells, playing a critical role in cochlear function. This cholinergic innervation originates in the superior olivary complex. ACh is also released in the auditory cortex (AC), where it modulates patterns of information flow and plays an important role in synaptic plasticity (e.g., Irvine, 2010; Metherate and Hsieh, 2004; Syka, 2002). Cholinergic innervation of the AC originates in the basal forebrain (Kamke et al., 2005). In between the AC and the cochlea are numerous nuclei of the central auditory pathways. Many of these nuclei are innervated by cholinergic axons (Henderson and Sherriff, 1991; Morley and Happe, 2000), but much less attention has been devoted to these circuits. Several recent reviews discuss cholinergic circuits and mechanisms associated with the cochlea or the AC (Xiong et al., 2009; Irvine, 2010; Metherate, 2010; Schofield, 2010b) or, in more general terms, with sensory systems and attention (e.g., Deco and Thiele, 2009). For this reason as well as space limitations, the present review is focused on cholinergic innervation of the subcortical central auditory pathway.

As demonstrated by this issue of Hearing Research, there is growing interest in plasticity in subcortical auditory nuclei. ACh has been implicated in some of this plasticity. For example, fear conditioning leads to plasticity in cells in the inferior colliculus (IC; Ji et al., 2001; Ji and Suga, 2003). This plasticity depends on ACh in the IC, but the source of the ACh was unclear. The following description focuses first on the source of cholinergic innervation of the IC, which we identified as two prominent groups of cholinergic cells in the tegmentum of the pons and midbrain¹. We then show that the same tegmental cholinergic nuclei innervate additional subcortical auditory structures. Finally, we show that the AC has direct inputs to the cholinergic brainstem cells, including cells that project directly to various auditory nuclei. The discussion is based largely on published data, although some new data are presented at appropriate points. The materials and methods for the new data are summarized in Section 8.

2. Cholinergic innervation of brainstem and thalamus

2.1. Acetylcholine in the IC

Curtis and Koizumi (1961) looked at ACh effects on spontaneous activity of IC cells. Application of cholinergic agents affected a small minority (28/273) of IC units. Perhaps as a result of this observation, ACh in the IC was largely ignored for many years. More recent studies looked at ACh effects on the responses of IC cells to acoustic stimuli, and found that ACh changes the responses of the majority (60–85%) of IC cells (Farley et al., 1983; Habbicht and Vater, 1996; Watanabe and Simada, 1973). The conclusion, then, is that ACh has little effect on the spontaneous activity of IC cells, but can affect the responses of most IC cells to sound stimuli. Such a pattern of effects can serve as a definition of a neuromodulator, and is consistent with cholinergic effects in other systems (e.g., Timofeeva et al., 2005). The widespread cholinergic effects are consistent with a distribution of nicotinic and muscarinic ACh receptors throughout the IC (Clarke et al., 1985; Glendenning and Baker, 1988; Morley and Happe, 2000; Rotter et al., 1979). It has been suggested that ACh enhances unit responses to specific stimuli (i.e., improves signal/noise ratio) and may set the level of excitability of IC cells in general or in association with particular stimuli (Farley et al., 1983; Habbicht and Vater, 1996; Miko and Sanes, 2009). The cholinergic effects are mediated, at least in part, by direct actions on GABAergic cells or synaptic terminals in the IC (Miko and Sanes, 2009; Yigit et al., 2003). Whether cholinergic axons contact non-GABAergic IC cells is not known. Interest in cholinergic innervation of the IC

¹There is a large degree of similarity in the distribution of cholinergic cells across species, although variations exist. We will use the terminology as described in Motts et al. (2008), which compares cholinergic cells in guinea pigs and other mammals and includes details on cholinergic cells in or around auditory nuclei.

has been expanded by the finding that blockade of muscarinic receptors in the IC interferes with some forms of plasticity (e.g., that induced by fear conditioning; Ji et al., 2001; 2005), but not with other forms of plasticity (e.g., that induced by pseudo-conditioning; Ji and Suga, 2009).

There is no evidence for cholinergic cells within the IC (Motts et al., 2008), so the cholinergic innervation must arise from extrinsic sources. We identified cholinergic inputs to the IC in guinea pigs by combining retrograde tracing with immunohistochemistry for choline acetyltransferase (ChAT), a specific marker of cholinergic cells (Motts and Schofield, 2009a). The experiments labeled ChAT-immunopositive cells in the pedunculopontine tegmental nucleus and the laterodorsal tegmental nucleus (PPT and LDT, respectively). The following sections describe these cholinergic nuclei and evidence for extensive connections between the cholinergic cells and many auditory structures.

2.2. Cholinergic cells of the pontomesencephalic tegmentum

The PPT and the LDT are prominent groups of cholinergic cells in the tegmentum of the pons and midbrain (Fig. 1). We will refer to the PPT and LDT collectively as the pontomesencephalic tegmentum, or PMT (Woolf and Butcher, 1989), and refer to distinctions between the PPT and LDT where appropriate. The PMT nuclei have widespread projections to the spinal cord, brainstem sensory and motor nuclei, reticular formation, thalamus, basal forebrain and frontal cortex (Garcia-Rill, 1991; Jenkinson et al., 2009; Jones, 2003; Smith et al., 1988; Steriade et al., 1988). The projections are associated with arousal, sensory gating, control of the sleep-wake cycle, orienting responses, and reward behavior (Chen et al., 2006; Pan and Hyland, 2005; Reese et al., 1995c; Rye, 1997; Swerdlow et al., 2001)². Among the earliest functions to be studied was the role of the PMT as part of the ascending reticular activating system. Stimulation of the PMT leads to an activated EEG pattern (Steriade et al., 1991). The cholinergic cells are active during waking and during paradoxical sleep (a.k.a. REM sleep), and less active during slow wave sleep (Boucetta and Jones, 2009). Their projections to the thalamus can alter the firing mode of thalamic relay cells, and thus modulate information flow in ascending pathways to the cerebral cortex. These projections terminate in most or all thalamic nuclei, including the medial geniculate body (MG), the auditory nucleus of the thalamus. In general, the similarities in the patterns of PMT projections to various thalamic nuclei led to assumptions of a common function across thalamic systems. However, the literature revealed possible differences between PMT projections to the MG versus other thalamic nuclei. The next section describes the apparent differences and new data that re-examine these issues.

2.3. Acetylcholine in the MG

Retrograde tracing in several species (rats, cats, macaques) shows that the cholinergic projection to most thalamic nuclei arises bilaterally in the PPT and LDT (Hallanger et al., 1987; Shute and Lewis, 1967; Steriade et al., 1988). The ipsilateral projection is predominant and, on each side, the PPT contributes more cells than the LDT. However, both retrograde and anterograde tracing experiments in rats suggest that there is no projection to the MG from the LDT (Cornwall et al., 1990; Hallanger et al., 1987; Satoh and Fibiger, 1986). The lack of a projection from the LDT to the MG suggests a unique cholinergic innervation for the auditory thalamus.

²An extensive literature describes connections between motor systems and the area occupied by the PPT. We refer the reader to recent reviews for discussion of the PPT and “midbrain extrapyramidal area” and “midbrain locomotor region” (e.g., Jenkinson et al., 2009; Takakusaki, 2008; Winn, 2008).

We combined retrograde tracing and immunohistochemistry to identify cholinergic projections to the MG in guinea pigs (Figure 2; Motts and Schofield, 2010). Retrogradely-labeled, immunopositive (i.e., cholinergic) cells were located in the PMT bilaterally. Contrary to expectations based on the rat experiments, our data in guinea pigs include a projection from cells in the LDT, revealing a cholinergic innervation of MG similar to that of other thalamic nuclei.

2.4. Collateral projections from cholinergic cells

The PMT contains a relatively small number of cells – about 40,000 cells in humans (Manaye et al., 1999); 7000 cells in guinea pigs (Leonard et al., 1995) and 6000 cells in rats (Jones, 1990). Given the widespread projections, perhaps it is not surprising that PMT cells often have collateral projections to multiple targets. Numerous studies in rats show that individual PMT cells project to the superior colliculus and the lateral geniculate nucleus (Billet et al., 1999), to the fastigial nucleus and rostral ventrolateral reticular nucleus (Ruggiero et al., 1997), or to the thalamic reticular nucleus and the cerebral cortex (Jourdain et al., 1989). One study suggests that individual PMT cholinergic cells can innervate bilaterally symmetrical targets (e.g., left and right lateral geniculate nuclei; Turlejski et al., 1994). Collateral projections could allow a small number of cells to 1) innervate a large number of targets, and, 2) to coordinate activity in those targets, and, possibly, 3) to enhance transmission of information through a pathway by modulating the responsiveness of cells at multiple points along the pathway. We found evidence for collateral projections to both ICs (Fig. 3A; Motts and Schofield, 2009a). We were interested in determining whether the PMT cells that project to the IC are the same ones that project to the MG. We tested this by combining multiple retrograde tracers with ChAT immunohistochemistry in guinea pigs (Motts and Schofield, 2009b).

We tested several possible patterns of projections to two targets: 1) to an MG and an IC on the same side of the brain; 2) to an MG and an IC on opposite sides; 3) to the left and right MGs. We found examples of each pattern. The most commonly observed pattern was from a PMT cell to the ipsilateral MG and ipsilateral IC (Fig. 3B). The second most common pattern was to the left and right MGs. Other patterns included cells that project to 3 targets (one IC and both MGs). We conclude that individual cholinergic cells can innervate bilateral targets as well as targets at different levels of the auditory pathways.

2.5. Acetylcholine in the cochlear nucleus (CN)

Cholinergic innervation of the CN is well established (Caspary et al., 1983; Comis and Whitfield, 1968; Fujino and Oertel, 2001; Godfrey et al., 1987, 2000; Happe and Morley, 1998; Henderson and Sherriff, 1991; Sherriff and Henderson, 1994). Sherriff and Henderson (1994) provide the only study in which retrograde tracers were injected into the CN and combined with immunohistochemistry to identify the source(s) of ACh. They identified cholinergic cells in the superior olivary complex, but not in the PMT, as the source of ACh in the CN of rats. We sought to expand the observations to guinea pigs, in which we had identified PMT connections to the IC and MG, and thus to provide a basis for contrasting within a single species the two auditory-related cholinergic systems in the brainstem (Motts and Schofield, 2005). The results were unexpected.

Injection of a retrograde tracer into the CN labeled many cells bilaterally in the superior olivary complex, in a pattern similar to that described in rats (Sherriff and Henderson, 1994). As expected, a subset of these cells were immunopositive for ChAT. In addition, there were a substantial number of retrogradely-labeled, ChAT-positive cells in the PMT. The PMT cells constituted about one quarter of the retrogradely-labeled, ChAT-positive cells. This result indicates that, at least in guinea pigs, the CN receives cholinergic innervation from

two different sources: the superior olivary complex and the PMT (Motts and Schofield, 2005). It also demonstrates that PMT cholinergic projections innervate the auditory pathways from the CN to the MG.

3. Evidence for inputs to PMT from sensory cortex

3.1. Inputs from auditory cortex

Several studies in rats focused on inputs to the PMT (Cornwall et al., 1990; Satoh and Fibiger, 1986; Semba and Fibiger, 1992; Steininger et al., 1992). Inputs from cerebral cortex originate in frontal and limbic areas. There had been no indications of inputs from the AC until, in the course of studying AC projections to other subcortical targets, we discovered direct projections from the primary auditory cortex (A1) to the PMT in guinea pigs (Fig. 4A, B; Schofield and Motts, 2009). One limitation of both the anterograde and the retrograde tracing studies is that they do not directly associate the inputs with the cholinergic cells in the PMT. We combined anterograde tracing from A1 with immunohistochemistry for ChAT in guinea pigs. We observed presumptive synaptic contacts between AC boutons and cholinergic cells in all the PMT nuclei (i.e., PPT and LDT, bilaterally). The results are the first report of AC projections to the PMT and, to the best of our knowledge, the first report to associate projections from any primary sensory cortical area with cholinergic cells in the PMT.

3.2. Lack of inputs from visual cortex

We were curious about the possibility that other primary sensory areas project to the PMT. In experiments not previously published, we made large injections of fluorescein dextran into the right visual cortex and FluoroRuby into the left visual cortex in each of two guinea pigs (see section 8 for Methods). Figure 4C-E shows a fluorescein dextran injection site and resulting label in the thalamus and the pontine nuclei. We could find no evidence for labeled axons in the PMT (Fig. 4F). This finding is consistent with previous studies of inputs to the PMT (Cornwall et al., 1990; Semba and Fibiger, 1992; Steininger et al., 1992). We conclude that the recently discovered projection to PMT from the AC is not representative of a general projection from all primary sensory cortices. Nevertheless, it may be of interest to use the same anterograde tracing methods that revealed AC projections to examine possible projections from higher order visual areas or other sensory regions (e.g., somatosensory cortex).

3.3. Cells of origin of cortical projections to the PMT

Retrograde tracers injected into the PPT labeled pyramidal cells in layer V of the AC, confirming the anterograde results and suggesting that the projection to the PMT is glutamatergic (Schofield and Motts, 2009). No labeled cells were present in the visual cortex, consistent with the results from the anterograde tracer injections described in the previous section.

4. Projections of PMT cholinergic cells that are contacted by AC axons

While our tracing studies suggested that AC axons contact PMT cholinergic cells, it left unclear which output pathways of the PMT were being contacted. As discussed above, the PMT projects to many targets, auditory and otherwise. We combined anterograde tracing and immunohistochemical staining with retrograde tracing from subcortical auditory structures to determine whether cholinergic cells that project to these auditory nuclei are among the targets of the AC axons. Figure 5 shows results from our first study, which focused on cholinergic projections to the IC (Schofield, 2010a). AC axons contacted cholinergic cells on both sides of the brainstem that project to the IC. The cholinergic cells

most often projected to the IC on the same side as the cholinergic cell body, but a small number projected to the contralateral IC. The origins of the AC projections from layer V pyramidal cells suggest that they would excite their cholinergic cell targets. Consequently, projections from one AC would likely lead to release of ACh bilaterally in the IC (Fig. 5C).

Future experiments will be needed to determine whether AC axons contact PMT cholinergic cells that project to other targets. Given the large number of PMT cells that project to the MG, we predict that some of these cells are contacted by AC axons. Preliminary data from guinea pigs, suggest that AC axons also contact PMT cholinergic cells that project to the CN (Schofield, 2011). Connections such as these would allow the AC to activate PMT cholinergic cells and, presumably, evoke release of acetylcholine at multiple points in the ascending auditory pathways.

5. Summary of the brainstem cholinergic circuitry

Figure 6 summarizes projections to auditory nuclei from cholinergic cells in the PMT and superior olivary complex. The widespread projections could support broad cholinergic actions across the auditory pathways. For some auditory structures, like the MG and the IC, the PMT is the primary or sole source of cholinergic inputs. In contrast, the CN receives inputs from cholinergic cells in both the PMT and the superior olivary complex.

Figure 6 also indicates the AC projections to each group of cholinergic cells – in both the PMT and the superior olivary complex - emphasizing the possibility that cortical activity could evoke release of acetylcholine in auditory structures from the cochlea to the MG. Note that the arrows indicate projections from one area to another; the target cells of a given arrow are known in only some instances. With regard to the PMT, we have shown that AC axons contact cholinergic cells that project to the IC or to the CN, but whether they contact PMT cells that project to the MG is unknown. AC axons also project to cholinergic cells in the superior olivary complex that project to the cochlea (Mulders and Robertson, 2000). These cholinergic cells innervate the CN via an axon collateral in addition to their defining projection to the cochlea (Brown, 1993). In the CN, then, one could predict cortically-activated release of ACh both through the superior olivary cells and through the PMT cells. An important step for future work will be to distinguish the contributions of these two cholinergic inputs to the CN.

6. Functional implications

The data indicate a broad and bilateral cholinergic projection from the PMT that is in a position to affect processing at many levels of the auditory system. The frequent occurrence of collateral branching supports the idea of a common function for projections to multiple targets. Nonetheless, the identity of the target cells in each structure and the wide range of cholinergic receptors that are expressed in the auditory system may allow for distinct cholinergic actions in different areas. In the thalamus, ACh acts to control firing mode and transfer of information to neocortex (e.g., McCormick, 1987). In the brainstem, ACh affects firing rate and neuronal excitability (e.g., Habbicht and Vater, 1996) and can increase or decrease responses to sensory stimuli (e.g., Caspary et al., 1983; Fujino and Oertel, 2001). The following speculations rely on suggestions from cholinergic actions in auditory structures, from an understanding of PMT cholinergic functions outside the “traditional” ascending auditory pathways, and from information on the responses of PMT cells to acoustic stimuli.

6.1. Habituation and novelty detection

Approximately half of the neurons in the PMT respond to auditory stimuli (Koyama et al., 1994; Reese et al., 1995a, b). Many PMT cells are also multimodal, responding to two or more sensory modalities (audition, touch and vision). The presence or absence of habituation (along with other distinctions) served to differentiate two populations of PMT cells. One population responded consistently to repeated stimuli and a second population responded only to the first one or two in a series of identical stimuli. This habituation may play an important role in an organism's ability to detect and attend to novel stimuli (Koyama et al., 1994). Interestingly, "novelty" neurons (a.k.a. neurons that show "stimulus-specific adaptation, or SSA") have been described recently in the IC (Malmierca et al., 2009; Pérez-González et al., 2005). A majority of IC cells show some degree of SSA. Those that show the strongest SSA have some intriguing similarities with PMT cells that habituate. First, these IC cells respond only at the onset of a stimulus, like the PMT cells. Second, both groups of cells show broad frequency tuning. If this form of adaptation in the IC depends on the PMT cholinergic input, one would predict that application of cholinergic blockers to the IC cell would eliminate the selectivity for novel stimuli (i.e., the IC neuron would either cease responding at all or would lose its adaptation and continue to respond to a repeated stimulus). Given the multimodal nature of many PMT cells, it would be interesting to determine whether a non-auditory stimulus – say, a flash of light embedded in a series of auditory stimuli – would overcome the habituation of an IC cell to the auditory stimulus (i.e., the cell would respond to the "same" auditory stimulus when it follows the flash of light), even if the IC cell did not respond directly to the visual stimulus.

6.2. Sensory gating

The PMT has also been associated with sensory gating. A popular model for studying gating is prepulse inhibition of the acoustic startle reflex. This reflex includes a blink, contraction of facial, neck and skeletal muscles, and an acceleration of heart rate in response to a sudden sensory stimulus (Koch, 1999). Startle can be induced by various modalities, including sight, sound and touch. For acoustic startle, the circuitry includes neurons in the CN that synapse onto cells in the caudal pontine reticular nucleus (PnC), which in turn contact cranial and spinal motor neurons that drive the motor response (Koch, 1999). The startle response can be inhibited by a less intense stimulus presented before the startling stimulus, a phenomenon known as prepulse inhibition of startle (Hoffman and Ison, 1980). This inhibition is mediated by projections of PMT cholinergic cells to the PnC (Bosch and Schmid, 2008; Koch, 1993; Swerdlow et al., 2001; Yeomans et al., 2006). It has been proposed that the prepulse inhibition allows the organism to continue processing sounds without the interruption that would be induced by a startle response (Graham, 1975). One can speculate that the PMT projections to structures in the ascending auditory pathways could enhance responsiveness or transmission of the sensory information during the time when the motor components of the startle are being inhibited. Wang et al., (2007) have shown that a "pre-pulse" of weak noise can alter response thresholds and frequency tuning of IC cells. These changes are dependent on GABAergic circuits in the IC. The possibility that cholinergic inputs to the IC can activate the same GABAergic circuits is supported by evidence that ACh activates IC GABAergic cells directly (Yigit et al., 2003).

Interestingly, "higher" functions can modulate prepulse inhibition of startle (Li et al., 2009). Both attention and emotional salience of the prepulse can affect the subsequent inhibition. Various forebrain areas, including the prefrontal cortex, AC and amygdala, have been implicated. Prefrontal cortex projects directly to the PMT (Sesack et al., 1989). The amygdala could potentially affect the PMT via direct projections or via projections to the superior colliculus or locus ceruleus. Finally, the AC projects to the IC (part of the circuit for prepulse inhibition) and, as shown previously, also projects directly to the PMT.

Deciphering the contributions of these inputs to sensory gating is an ongoing challenge. One reason for continued interest in this issue is the well-documented abnormalities in sensory gating in such disorders as schizophrenia (Braff et al., 2001; Geyer et al., 2001). Continued advancement in identifying cholinergic circuits and the descending pathways that modulate them may be particularly important for understanding sensory processing in various disorders.

6.3. Motivation and reward

The PMT may serve as an interface between sensory and motivational systems (Pan and Hyland, 2005). The PMT has been associated with reward behaviors, including conditioned place preference, intravenous drug self-administration, and intracranial electrical self-stimulation (Chen et al., 2006). An important part of the PMT circuitry related to reward is the pathway from cholinergic PMT cells to dopaminergic cells in the ventral tegmental area (Chen et al., 2006; Pan and Hyland, 2005). It would be interesting to determine whether PMT cells that participate in reward behaviors project to auditory nuclei. For example, do individual cells project to both the ventral tegmental area and the auditory thalamus or midbrain? Such projections may help to identify locations in the auditory pathways where reward signals are integrated with sensory processing.

6.4. Arousal

The cholinergic projections to the thalamus have been associated with arousal and control of the sleep-wake cycle. It seems likely that PMT projections to other auditory structures could serve a similar function. Velluti and colleagues have shown that the responses of neurons at many levels of the auditory system change as an animal passes from waking to slow-wave sleep to paradoxical sleep (Goldstein-Daruech, 2002; Pedemonte et al., 1994; Peña et al., 1992, 1999). These results demonstrate the continued processing of acoustic stimuli even while an individual sleeps.

A loud sound could presumably activate the PMT and lead to waking of a sleeping individual or increased vigilance in an awake individual. As discussed above, PMT projections may contribute to novelty detection, or stimulus specific adaptation, in auditory nuclei. The novelty of a stimulus may itself be a factor in inducing arousal, including waking from sleep (Ruby et al., 2008). Several additional aspects of arousal are of interest in view of the descending projections from forebrain to the PMT. The salience of a stimulus clearly affects the ability of a stimulus to arouse or to capture attention. This may occur in the cocktail party effect, whereby a signal, such as one's name, "pops out" of the background noise and can redirect a listener's attention. A similar phenomenon occurs during sleep, when a person's own name is more effective at waking him or her than someone else's name (Oswald et al., 1960; Bastuji et al., 2002). It seems likely that cholinergic projections from the PMT to the auditory nuclei could play a role in these aspects of arousal and attention.

6.5. Top-down effects and attention

An area of particular interest concerns the broad descending projections from the AC that terminate directly at all levels of the central auditory system (reviewed by Schofield, 2010b). These pathways provide a basis for top-down effects on auditory processing, allowing the AC to modify how sounds are analyzed and to control how, and what, information ascends to higher levels. Functions attributed to this pathway include binaural processing (Nakamoto et al. 2008), encoding of stimulus frequency, timing and amplitude (Suga 2008; Xiong et al. 2009) and behaviorally-driven learning (Bajo et al. 2010). The underlying mechanisms are only beginning to be identified, and may include plasticity at both cortical and subcortical levels (Suga 2008; Winkowski and Knudsen 2008; Xiong et al. 2009; He and Yu 2010).

Knudsen and colleagues emphasized the association between cholinergic systems and mechanisms of attention that could be particularly relevant for experience-dependent plasticity (e.g., Keuroghlian and Knudsen, 2007; Winkowski and Knudsen, 2008). The projections from the AC to brainstem cholinergic cells that project to subcortical auditory nuclei could assure that ACh is released concurrent with the direct effects of corticofugal activity in those auditory nuclei. It is interesting to note in this context that cholinergic projections appear to terminate in the major sites targeted by direct AC projections (i.e., the MG, IC and CN). More experiments are needed to explore the relationships of the cholinergic inputs and activity in the corticofugal pathway.

6.6. Tinnitus

A maladaptive form of plasticity may underlie tinnitus, a common condition that has been associated with changes - usually an increase but in some cases a decrease - in the firing rates of neurons in several auditory areas (Brozoski et al., 2002; 2005; Eggermont and Kenmochi, 1998; Kaltenbach and Afman, 2000; Norena and Eggermont, 2003; Salvi et al., 2000; Tzounopoulos, 2008). Animal models of tinnitus demonstrate changes in cholinergic mechanisms in auditory nuclei (e.g., Jin et al., 2006). Interestingly, ACh has been suggested to adjust excitability and set the level of activity in the IC (Farley et al., 1983; Habbicht and Vater, 1996), one of the regions reported to show hyperactivity in tinnitus. Miko and Sanes (2009) recently concluded that ACh could affect IC excitability via actions on GABAergic IC cells. Could hyperactivity associated with tinnitus be a result of the cholinergic system trying to “reset” the responsiveness of the auditory system broadly (i.e., across frequencies), with a result that a subset of cells (those associated with the frequencies of the tinnitus) become hyper-excitable? A better understanding of the mechanisms of actions of ACh on excitatory vs. inhibitory cells will be of particular interest in this regard.

7. Future work

There are undoubtedly roles for ACh beyond those discussed above. Plasticity is likely to be important in normal development and aging as well as in response to injury (Holt et al., 2005; Morley and Happe, 2000; Morley et al., 2004; Raza et al., 1994). It may be particularly relevant that PMT cholinergic cells are capable of generating nitric oxide, a gaseous molecule implicated in neuronal excitability and plasticity, which may be a factor at some or all of the cholinergic PMT terminals (Steinert et al., 2010; Vincent, 2000). While this review has focused on cholinergic circuitry, there is increasing appreciation for the roles of non-cholinergic projections from the PMT (Boucetta and Jones, 2009; Wang and Morales, 2009). The non-cholinergic cells can provide a substantial proportion of the projections from the PMT to a given target (e.g., to the MG; Motts and Schofield, 2009). Finally, ACh is only one of several neuromodulators, such as serotonin and noradrenaline, that affect auditory processing (Altschuler and Shore, 2010; Behrens et al., 2002; Caspary et al., 2008; Hurley, 2010; this issue; Hurley et al., 2004; Klepper and Herbert, 1991; Miko and Sanes, 2009; Tong et al., 2005). An exciting area for future work will be to identify the interactions between these various modulators and their effects on processing of auditory information.

It remains to be determined whether, or to what extent, the LDT and the PPT have distinct functions. Some recent studies have focused on the possibility of functional subdivisions *WITHIN* the PPT. In some cases, there are differences proposed for spatially separate parts of the PPT, whereas in other cases the emphasis is on distinct functions for cells that use different neurotransmitters (i.e., cholinergic vs. non-cholinergic cells; e.g., Winn, 2008; Mena-Segovia et al., 2009). Interestingly, many of these studies focus on motor functions of the PPT and interconnections with basal ganglia (and, to a lesser extent, other motor structures; e.g., Jenkinson et al., 2009). It will be of great interest in future studies to

determine the extent to which motor and auditory (or other sensory) functions overlap or integrate in the PMT nuclei.

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List of Abbreviations

5n	trigeminal nerve
AC	auditory cortex
ACh	acetylcholine
APT	anterior pretectal nucleus
Aq	aqueduct
Cb	cerebellum
ChAT	choline acetyltransferase
cIC	contralateral inferior colliculus
CN	cochlear nucleus
D	dorsal
dl	dorsolateral MGI
DLL	dorsal nucleus of the lateral lemniscus
FD	fluorescein dextran
IC	inferior colliculus
iIC	ipsilateral inferior colliculus
ILL	intermediate nucleus of the lateral lemniscus
iMG	ipsilateral medial geniculate body
L	lateral
LDT	laterodorsal tegmental nucleus
lfp	longitudinal fasciculus of the pons
ll	lateral lemniscus
m	medial MG
MG	medial geniculate body
PAG	periaqueductal gray
PMT	pontomesencephalic tegmentum
Pn	pontine nuclei
PnC	caudal pontine reticular nucleus
PnO	pontine reticular nucleus, oral part
PPT	pedunculopontine tegmental nucleus

s	shell subdivision of MG
sg	suprageniculate MG
SN	substantia nigra
v	ventral MG
VC	visual cortex
VLL	ventral nucleus of the lateral lemniscus

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8. Appendix: Materials and methods for anterograde tracing from visual cortex

All experiments were done with approval of the Institutional Animal Care and Use Committee and according to National Institutes of Health Guide for the Care and Use of Laboratory Animals. The experiments were performed on two adult, pigmented guinea pigs (Elm Hill Labs). The methods match those used for anterograde labeling of axons from auditory cortex to the PMT (Schofield and Motts, 2009), except that the anterograde tracers were injected in visual cortex instead of auditory cortex. Visual cortex was localized according to maps in the guinea pig (Wree et al., 1981). FluoroRuby was injected into the left cortex and fluorescein dextran was injected into the right cortex in each animal.

Figure 1.

The pontomesencephalic tegmentum. **A)** Plot of a transverse section containing PMT. Each black dot represents one ChAT+ cell in PMT. The superior cerebellar peduncle (scp; **shaded gray**) serves as a reference point for the PMT. **B)** Photomicrograph of ChAT-immunolabel in the left PMT; dotted line indicates the scp. **C, D)** Photomicrographs of labeled cells in the PPT (**C**) and LDT (**D**). 5n; trigeminal nerve; Aq; aqueduct; D, dorsal; DLL, dorsal nucleus of the lateral lemniscus; IC, inferior colliculus; ILL, intermediate nucleus of the lateral lemniscus; L, lateral; LDT, laterodorsal tegmental nucleus; Ifp, longitudinal fasciculus of the pons; II, lateral lemniscus; PAG, periaqueductal gray; Pn, pontine nuclei; PnO, pontine reticular nucleus, oral part; PPT, pedunclopontine tegmental nucleus; VLL, ventral nucleus of the lateral lemniscus. Scale bars = 1 mm for A; 0.5 mm for B; 10 μ m for C, D. Adapted from Motts et al., 2008, with permission.

Figure 2.

Photomicrographs of representative tracer injections into MG (A and B) and labeled cells in the PMT (C and D). **A)** Injection of green beads confined to the ventral subdivision of MG. The fluorescence image is overlaid with a brightfield image showing the cytochrome oxidase stain used to visualize MG subdivisions. GP 587. **B)** An injection of red beads within the suprageniculate subdivision. GP 586. **C, D)** the left image shows PPT cells labeled with green beads (projecting to the ipsilateral MG); the right image shows the same field of view visualized for ChAT immunolabel. Arrowheads indicate cells labeled with both tracer and immunolabel; arrows indicate a cell labeled with tracer only. dl-dorsolateral; m-medial; s-shell; sg-suprageniculate; v-ventral. Scale bars = 0.5 mm for A, B; 10 μ m for C, D. Adapted from Motts and Schofield, 2010, with permission.

Figure 3.

Cholinergic PMT cells that project to more than one auditory target. Each column shows a single field of view visualized for different labels. Arrowheads indicate triple labeled cells. **A)** A cell in the left PPT labeled by red beads injected into the ipsilateral IC (iIC; top panel), by FluoroGold injected into the contralateral IC (cIC), and by ChAT immunostaining (AlexaFluor 488; bottom panel). **B)** A cell in the left LDT labeled by green beads injected into the ipsilateral MG (iMG, top panel), by Fast Blue injected into the ipsilateral IC (iIC, middle panel), and by ChAT immunostaining (AlexaFluor647; bottom panel). Scale bars = 10 μ m. Panel A from Motts and Schofield, 2009a, with permission.

Figure 4. Labeled cortical axons after injections into the auditory cortex (AC) or visual cortex (VC). **A, B**) FluoroRuby-labeled axons in PMT after injection in the ipsilateral AC. Boutons were associated with thin axons (arrows) and thick axons (arrowheads). **C**) Dorsal view of a guinea pig brain showing a fluorescein dextran (FD) injection site in right visual cortex. The fluorescent image (gray rectangle) was taken with a fluorescence microscope and digitally overlaid with an image of the whole brain taken with a digital camera and macro lens. The red discoloration around the “VC” label is from an injection of FluoroRuby into the left VC. **D**) FD label in the thalamus after the injection in C. The lateral geniculate nucleus (LG, enlarged in inset) contained labeled cells (arrowheads) among many labeled axons. Labeled cells (arrows) were also visible in the lateral posterior nucleus (LP). **E**) FD-labeled axons in the pontine nuclei after the injection in C. **F**) PPT with no visible axons labeled after injection of the ipsilateral VC. Scale bars = 10 μ m in A, B, E, F; 2 mm in C; 0.5 mm in D. APT, anterior pretectum; Cb, cerebellum; MG, medial geniculate body; SN, substantia nigra; VC, visual cortex. Panels A and B adapted from Schofield and Motts, 2009, with permission.

Figure 5.

A. Left column (“Retrograde”): Photomicrograph of a cell (arrowhead) in the left PPT that was labeled by Fast Blue injected into the left inferior colliculus (IC). Middle column (“ChAT”): The same cell (arrowhead) visualized for ChAT immunostaining. Third column (“Antero/retro”): overlay of the retrograde label with an image of the axons (red) labeled by an injection of FluoroRuby into the left auditory cortex (AC), showing cortical boutons in close contact (arrows) with a dendrite of the labeled cell. **B.** Same conventions as A, except that the cell is in the right PPT and the Fast Blue was injected into the right IC. **C.** Summary diagram. Red triangles represent layer V pyramidal cells that give rise to descending projections (red arrows) to the PPT and LDT. Blue arrows represent cholinergic cells that were contacted by cortical axons and that project to the IC (a thicker arrow means more contacts were associated with that pathway). Labels “A” and “B” indicate the pathways represented by the cells in panels A and B. Adapted from Schofield (2010a), with permission.

Figure 6.

Schematic diagram summarizing projections of the brainstem cholinergic cells and relevant cortical connections. The sections are modeled after transverse sections in guinea pigs, with key auditory areas shaded. Cholinergic projections from the pontomesencephalic tegmentum (PMT) are shown in red; those from the superior olivary complex are shown in green. Glutamatergic projections from the auditory cortex to the cholinergic cell groups are shown in blue. Branched arrows indicate population projections, not the pattern of branching for individual axons. The diagram is based primarily on results from guinea pigs and rats (see studies cited in text). PnC – caudal pontine reticular nucleus.