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Review

Serotonin in the inferior colliculus

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Abstract

It has been recognized for some time that serotonin fibers originating in raphe nuclei are present in the inferior colliculi of all mammalian species studied. More recently, serotonin has been found to modulate the responses of single inferior colliculus neurons to many types of auditory stimuli, ranging from simple tone bursts to complex species-specific vocalizations. The effects of serotonin are often quite strong, and for some neurons are also highly specific. A dramatic illustration of this is that serotonin can change the selectivity of some neurons for sounds, including species-specific vocalizations. These results are discussed in light of several theories on the function of serotonin in the IC, and of outstanding issues that remain to be addressed.

Key words: 5HT, 5-hydroxytryptamine (serotonin); IC, inferior colliculus

1. Introduction

A common and useful model for viewing the workings of the inferior colliculus (IC) is as a collection of hard-wired circuits. This concept has been key in directing research in the IC. Exploration of auditory brainstem circuitry has revealed many of the numerous ascending and descending pathways to the IC and its subnuclei (for example Brugge, 1992; Irvine, 1992; Oliver and Huerta, 1992). Imposed upon this hard-wired circuitry, however, are inputs from many different neuromodulatory systems originating in classically non-auditory regions of the brain. Among the panoply of neuromodulators in the IC are the indoleamine 5-hydroxytryptamine (5HT or serotonin) (Kaiser and Covey, 1997; Klepper and Herbert, 1991; Steinbusch, 1981; Thompson et al., 1994; Hurley and Thompson, 2001), the catecholamines dopamine (Paloff and Usunoff, 2000; Olazábal and Moore, 1989) and noradrenaline (Klepper and Herbert, 1991; Moore and Bloom, 1979; Wynne and Robertson, 1996), acetylcholine (Henderson and Sherriff, 1991), and peptide modulators such as cholecystokinin (Fallon and Seroogy, 1984; Wynne et al., 1995), somatostatin (Wynne et al., 1995; Wynne and Robertson, 1997) and substance P (Nakaya et al., 1994; Wynne et al., 1995; Wynne and Robertson, 1997).

The neuromodulator in the IC which has received the most attention is serotonin (Hurley and Thompson, 2001; Kaiser and Covey, 1997; Klepper and Herbert, 1991; Steinbusch, 1981; Thompson et al., 1994). Serotonin is a neuromodulator which in other sensory and motor systems has been shown to have profound effects on neural processing, functionally reconfiguring the circuitry within these systems (i.e. Bassant et al., 1990; Eaton and Salt, 1989; Mooney et al., 1996; Rogawski and Aghajanian, 1980; Sillar et al., 1998; Waterhouse et al., 1986). In this review we bring together different sources of information on the projection patterns, sources, and effects of serotonin on the response properties of IC neurons, and discuss their potential relevance to existing theories of serotonin function.

2. Serotonin in the IC

Various histological techniques have all confirmed the presence of serotonin in the IC, and provide some

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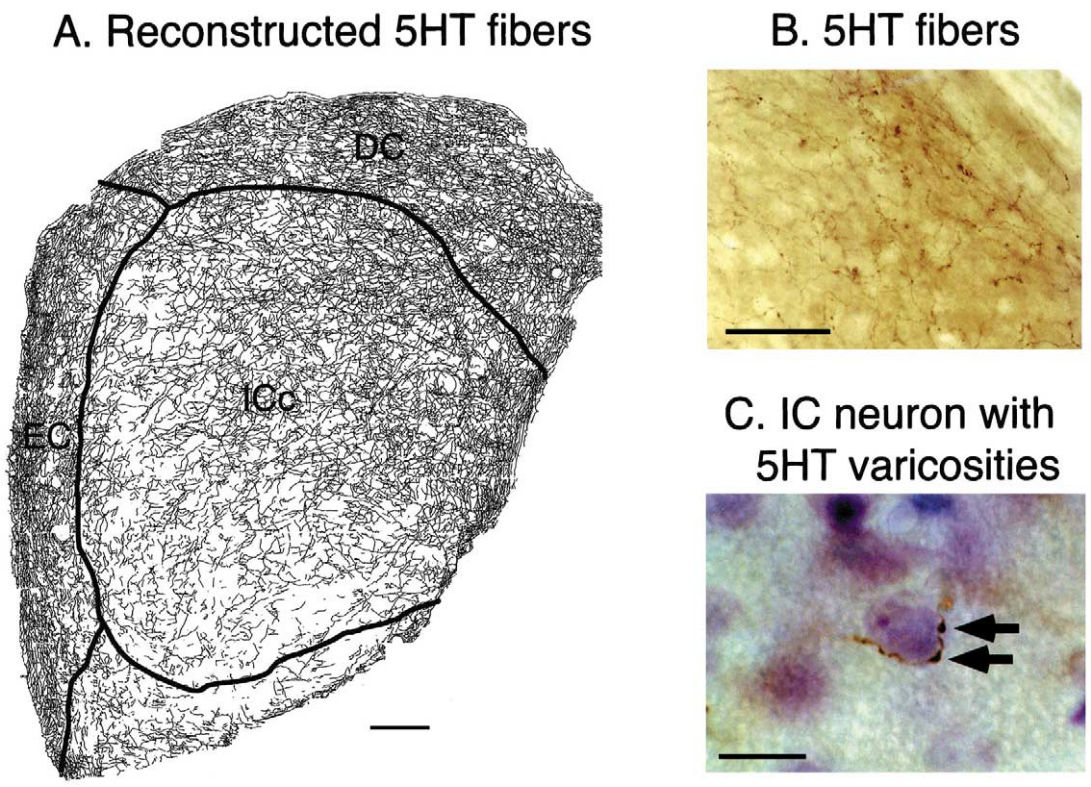

Fig. 1. Anatomy of serotonin in the IC. (A) A camera lucida reconstruction of all of the serotonergic fibers from one section of the brain of a Mexican free-tailed bat. The pattern of fiber density is similar in other mammals. (B) Photomicrograph of serotonin fibers from the dorsal cortex of the IC of bat which have been visualized immunohistochemically. (C) A close-up of serotonin-containing varicosities (indicated by arrows) immediately apposed to a counter-stained cell body in the IC. Scale bars = 100 μm in A, 20 μm in B, 10 μm in C. DC = dorsal cortex, EC = external cortex, ICc = central IC, 5HT = 5-hydroxytryptamine = serotonin. This figure was adapted from Hurley and Thompson, 2001.

of the strongest evidence for its endogenous modulation of neurons. These techniques range from histofluorescence (Fuxe, 1965) and immunohistochemistry (Klepper and Herbert, 1991; Thompson et al., 1994; Hurley and Thompson, 2001; Kaiser and Covey, 1997), to in vivo measurement of serotonin using the techniques of microdialysis (Adell et al., 1991) and high-performance liquid chromatography (Cransac et al., 1998). Serotonin receptors are also present in the IC. These postsynaptic receptors have been measured by the binding of radioactive receptor-specific ligands, as well as by mRNA and immunohistochemical labeling techniques. Serotonin receptors fall into seven main families, and members of four of these, the 5HT1 (Chalmers and Watson, 1991; Pompeiano et al., 1992; Thompson et al., 1994; Wright et al., 1995), 5HT2 (Wright et al., 1995; Harlan et al., 2000), 5HT4 (Waeber et al., 1994), and 5HT7 (To et al., 1995) families, have been found in the IC.

While serotonin fibers are found in all subdivisions of the IC, they are not distributed uniformly (Fig. 1A,B; Hurley and Thompson, 2001; Kaiser and Covey, 1997; Klepper and Herbert, 1991; Thompson et al., 1994). Fibers are most dense in the dorsal cortex and external nucleus of the IC, and they are less dense in the central nucleus of the IC, especially in a ventromedial region. This basic pattern of serotonergic fibers is highly conserved among mammalian species, with similar staining patterns reported for two bat species, cat, rat, guinea pig, and bush baby (Hurley and Thompson, 2001; Kaiser and Covey, 1997; Klepper and Herbert, 1991; Thompson et al., 1994). Some serotonin receptor subtypes are also distributed non-uniformly. The serotonin 1C receptor has its greatest density in the external cortex of the IC (Wright et al., 1995), while the serotonin 1A receptor is densest in the posterior pericentral and dorsomedial subdivisions (Thompson et al., 1994), and the serotonin 7 receptor is densest in the dorsal cortex (To et al., 1995). In general, then, receptor density seems to follow the density of serotonin fibers.

Associated with serotonin fibers are periodic swellings or varicosities having the beads-on-a-string morphology typical of en passant synapses. Some of these varicosities are closely apposed to counter-stained cells at the light microscopic level, suggesting that they are associated with these cell bodies in a synaptic relationship (Fig. 1C; Hurley and Thompson, 2001), though this has not been confirmed at the electron microscopic level. In other parts of the brain, serotonin is thought to

be released from these varicosities at a slight distance from postsynaptic terminals compared to classical neurotransmitter synapses, in a process known as volume release (Beaudet and Descarries, 1978; Bunin and Wightman, 1998; Vergé and Calas, 2000).

3. Origin of serotonin fibers

Most of the serotonergic neurons innervating the IC originate in the dorsal raphe nucleus, though a few are found in other raphe nuclei (Klepper and Herbert, 1991). Raphe nuclei are found along the midline of the brain from the medulla to the midbrain (Dahlstrom and Fuxe, 1964). Most, though not all, serotonergic neurons are associated with this chain of raphe nuclei; some serotonergic neurons are found more laterally (Jacobs and Azmitia, 1992). Though raphe nuclei contain many serotonergic neurons, they also contain neurons with other transmitter phenotypes, including GABA, substance P, and enkephalin (Chan-Palay, 1981; Grobecker, 1983; Bowker et al., 1983; Araneda et al., 1989; Tanaka et al., 1993). Some of these other transmitters are even found in serotonergic neurons as cotransmitters (i.e. Chan-Palay, 1981; Bowker et al., 1983; Araneda et al., 1989; Magoul et al., 1988).

Serotonergic neurons of the dorsal raphe project broadly across the forebrain, innervating many regions besides the IC. These regions include auditory and non-auditory cortices (Azmitia and Segal, 1978; Bobillier et al., 1975; Jacobs and Azmitia, 1992; Moore et al., 1978), as well as brainstem auditory nuclei like the cochlear nucleus and nuclei of the superior olivary complex (Klepper and Herbert, 1991; Thompson and Thompson, 2001; Thompson et al., 1995). Individual serotonergic neurons may even send collaterals to widely divergent regions of the brain, such as cortical and subcortical somatosensory regions (Petrov et al., 1992; Allen and Cechetto, 1994; Kirifides et al., 2001; Li et al., 2001).

Serotonergic release in the IC is potentially modulated by behavioral state and external sensory cues. In cats, the level of tonic activity of dorsal raphe neurons varies with the sleep–wake cycle, with cells firing at a higher rate during wakefulness and at a lower rate during sleep, especially during REM sleep (Trulson and Jacobs, 1979). Some dorsal raphe neurons also fire in conjunction with oral-buccal movements (Fornal et al., 1996). In addition, flashes of light and auditory stimuli can transiently activate or reset the firing of a large proportion of dorsal raphe neurons, so that sensory stimuli reliably trigger action potentials (Heym et al., 1982; Rasmussen et al., 1986; Trulson and Trulson, 1982). Anatomical connections that would support sensory responses by dorsal raphe neurons include a projection from a previously unidentified region near the cochlear nucleus and flocculus. This region is thought to be multisensory and is called the juxta-acousticofloccular fascicle (Ye and Kim, 2001).

4. Effects of serotonin in the IC

In this section we review evidence showing that exogenously applied serotonin strongly affects the responses of IC neurons to both simple tone bursts and to more complex, behaviorally relevant types of sounds. The experiments on which this section is based were performed mainly in Mexican free-tailed bats, which possess an excellent sense of hearing as well as a rich repertoire of communication and echolocation calls (Balcombe and McCracken, 1992; Gelfand and McCracken, 1986; Simmons et al., 1978, 1979). The types of complex sounds used in these studies are fre-

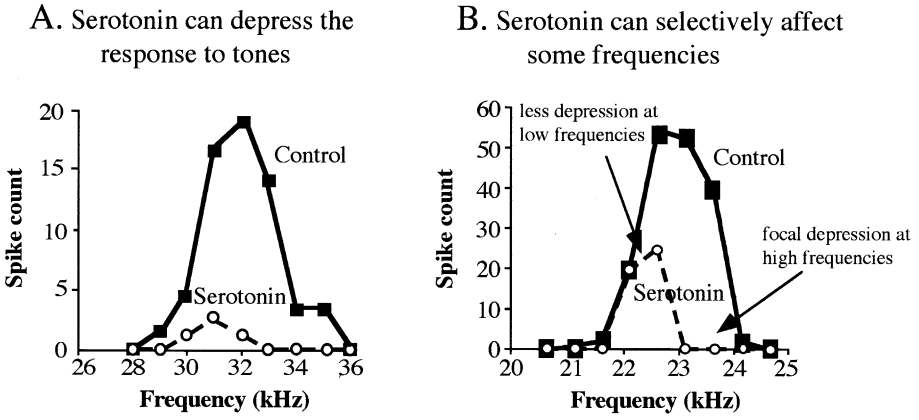

Fig. 2. The effects of iontophoresed serotonin on the responses of single IC neurons to tone bursts. (A) Serotonin affects the responses to tones across one neuron's entire frequency range equally, depressing the overall response dramatically. (B) Serotonin affects the responses of one neuron by depressing the responses to some frequencies entirely, but affecting the responses to other frequencies less. This figure was adapted from Hurley and Pollak, 2001.

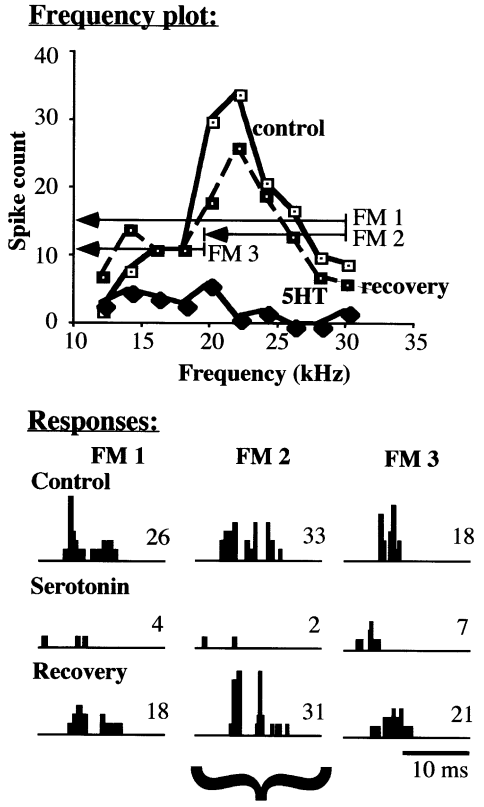

Fig. 3. Serotonin effects on frequency tuning and on the responses to FM sweeps are linked in neurons broadly affected by serotonin. At the top is a frequency plot for a single IC neuron illustrating that serotonin decreased the responses across the neuron's entire frequency range. Diagrams of three downward FM sweeps spanning different frequency ranges are superimposed on this plot. Below are plotted the peristimulus time histograms for the same neuron's response to all three FM sweeps in the control, serotonin, and in recovery. Serotonin suppressed the responses to all three sweeps. This figure was adapted from Hurley and Pollak, 2001.

quency-modulated (FM) sweeps and recorded species-specific vocalizations (Hurley and Pollak, 2001). These sorts of complex sounds are of interest because they more closely approximate sounds produced during behavior than do tone bursts. Here, we will focus primarily on responses to FM sweeps. FM sweeps are elements of the vocalizations of many animals (e.g. Kanwal et al., 1994; Bieser, 1998; Shipley et al., 1991). Downward FM sweeps have particular relevance for bats since they are similar in structure to the echolocation calls of many bats (for example Simmons et al., 1978, 1979, 1996; Kanwal et al., 1994).

One of the major effects of serotonin is to control the gain of the responses of IC neurons, which occurs in about 75% of serotonin-responsive neurons (Hurley and Pollak, 2001). In the majority of neurons, the gain control is downward, with serotonin depressing the responses of the neurons to tones across their entire frequency range (Fig. 2A). For a few neurons, the gain control is positive, with serotonin increasing the responses to the same wide array of tones. In an interesting minority of about 25% of serotonin-responsive neurons, however, serotonin does not simply act as a gain control but instead alters the way the neurons filter sound. Serotonin does this by selectively targeting responses to some frequencies, but leaving responses to other frequencies relatively unaffected, as can be seen in Fig. 2B. The net result of these changes is that serotonin skews the range of frequencies to which these neurons are sensitive, changing their frequency tuning. Both of these types of serotonin effects, on gain control and frequency tuning, have consequences for the responses of neurons to FM sweeps and to species-specific communication calls. The next two figures illustrate these consequences for responses to FM sweeps.

In Fig. 3 is an example of a neuron for which serotonin had a gain control effect, decreasing the response

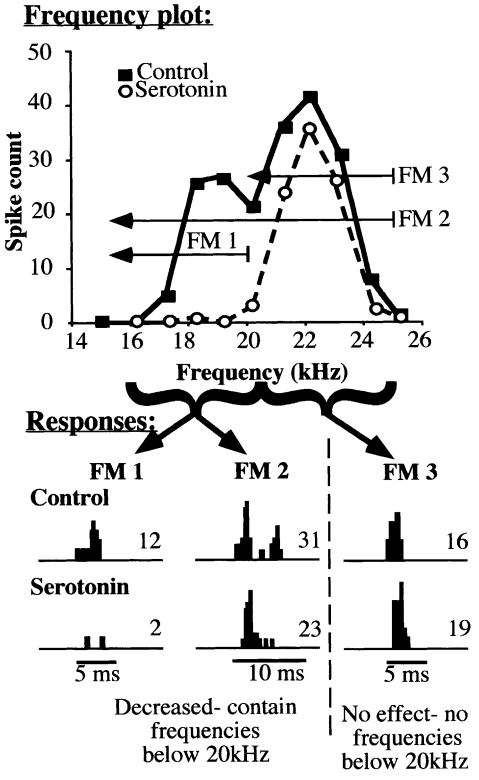

Fig. 4. Serotonin effects on frequency tuning and on the responses to FM sweeps are linked in neurons focally affected by serotonin. At the top is a plot of one neuron's frequency range; serotonin decreased responses at low frequencies but not at high frequencies. Superimposed on the plot are representations of three different FM sweeps spanning different frequency ranges. Below are the responses to the same FM sweeps. The response to FM sweep 1, confined to the lowest frequencies, was strongly decreased by serotonin. The response to FM sweep 2, spanning all frequencies, was slightly decreased by serotonin. The response to FM sweep 3, confined to the unaffected high frequencies, was not decreased by serotonin. This figure was adapted from Hurley and Pollak, 2001.

across its entire frequency range. The neuron in this figure also responded to three FM sweeps, differing in the range of frequencies they spanned, which can be seen superimposed on the frequency tuning plot. Serotonin decreased the responses to all of these FM sweeps, in keeping with its broad suppression of tones in the same neuron.

In Fig. 4 is an example of a neuron for which serotonin changed the frequency tuning, removing the response to lower frequencies but keeping the response to higher frequencies intact. These very focal changes in frequency tuning altered the range of FM sweeps that elicited a response from this neuron. In the control condition, this neuron also responded to three different FM sweeps. As expected, serotonin removed the response to the FM sweep that contained only the frequencies affected by serotonin (FM1). At the same time, serotonin slightly decreased the response to the FM sweep spanning both affected and unaffected frequencies (FM2), and had no effect on the response to the FM sweep containing only unaffected frequencies (FM3). When the responses to all three FM sweeps in the control and in serotonin are compared, it can be seen that serotonin changed the range of FM sweeps to which the neuron responded. That is, while the neuron responded to all three FM sweeps in the control, it responded to only two in serotonin. This close correspondence between the frequency specificity of serotonin effects and the effects of serotonin on the responses to both FM sweeps and species-specific calls is seen in most IC neurons.

Thus, for most neurons, the rules governing the relationship between serotonin effects on frequency tuning and on responses to complex sounds are straightforward. If serotonin affects the responses to tones within a certain frequency range, then it also affects the responses to FM sweeps and vocalizations that contain these frequencies, and has no effect on the responses to sounds which do not contain the affected frequencies.

However, in a small but intriguing group of neurons, there is no obvious correspondence between serotonin effects on frequency tuning and on the responses to complex sounds. An example is shown in Fig. 5. In the control, this neuron was selective for one recorded bat vocalization (Call A1) out of an array of 17, and thus did not respond to 16 other vocalizations that were played in this experiment. When serotonin was added, the neuron stopped responding to Call A1, but at the same time became selective for another vocalization (Call D2). Both vocalizations contain energy within the neuron's frequency range, as indicated by the dotted lines in the spectrograms (frequency versus time plots) in Fig. 5. The decrease in the response to Call A1 correlates with the general suppression of the response to tones which can be seen in the frequency plot at the top

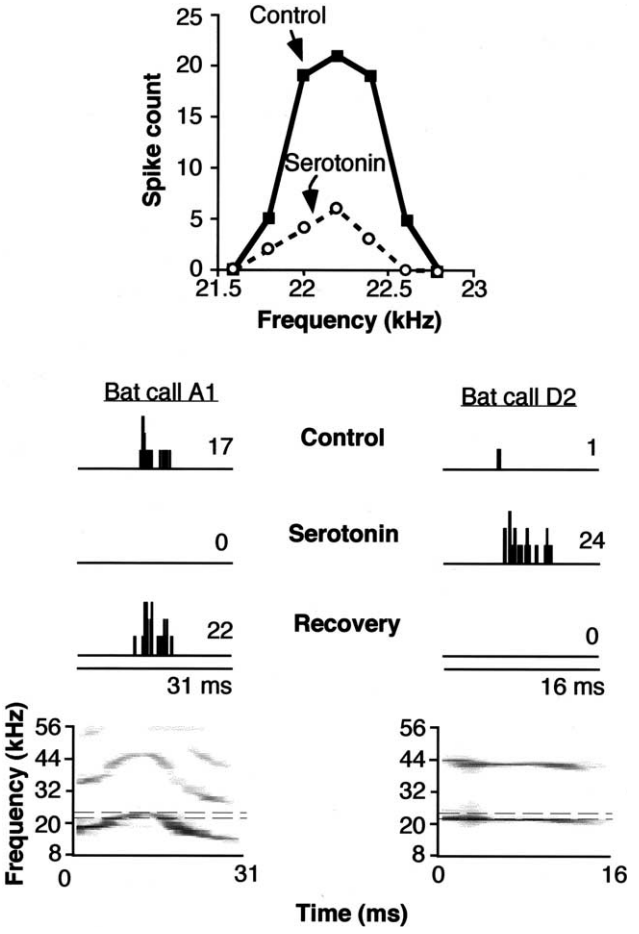

Fig. 5. Serotonin effects on frequency tuning and on the responses to complex sounds are not always linked. The frequency plot at the top shows that serotonin suppressed the responses across the entire frequency range of this neuron. Below are plotted the responses to two species-specific vocalizations and the spectrograms of these vocalizations. Dashed lines indicate the frequency response range of the neuron relative to the vocalizations. In the control, the neuron responded only to the first vocalization, but in serotonin, it responded only to the second vocalization. This figure was adapted from Hurley and Pollak, 2001.

of the figure. However, the increase in the response to Call D2 cannot be explained by referring to the frequency plot, since the frequency plot shows no increase of response at any frequency. For this neuron, as for other neurons in this class, serotonin effects do not correlate with frequency tuning and must be due to some unobserved variable.

Besides altering the magnitude of responses to sounds, serotonin also changes response latencies in some IC neurons. These sorts of changes have potential implications for a number of latency-dependent aspects of auditory processing, including binaural integration, coincidence detection, the shaping of the duration and timing of a response, and sound localization (for example Irvine et al., 1995; Ehrlich et al., 1997; Covey and Casseday, 1999; Park and Pollak, 1993; Park et al.,

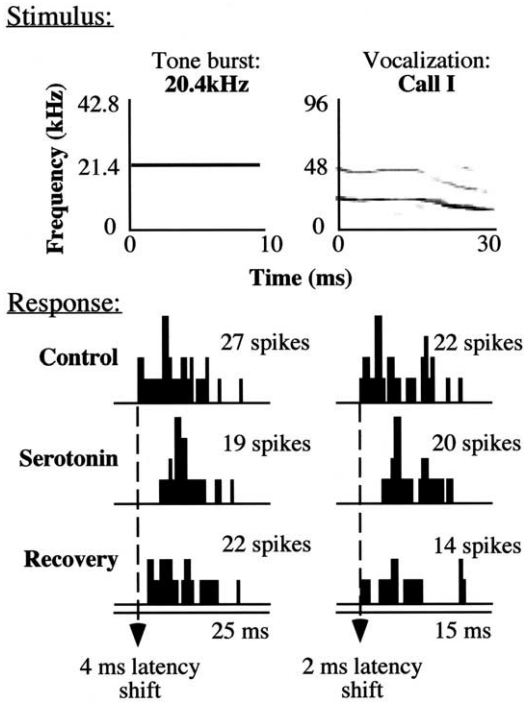

Fig. 6. Serotonin changes the latencies of the responses of some IC neurons to tones and recorded vocalizations. For this single IC neuron, serotonin increased the response latency to a 20.4-kHz tone by 4 ms and increased the response latency to a recorded vocalization, Call I, by 2 ms.

1996; Galazyuk and Feng, 2001). An example is shown in Fig. 6. For this neuron, serotonin increased the latencies of responses to tone bursts and recorded vocalizations by as much as 4 ms. A change on this scale could have dramatic effects for the processing of sounds.

In summary, serotonin dramatically transforms the firing of many IC neurons in response to auditory stimuli. Serotonin affects the responses to both tone bursts and to more complex sounds, including species-specific vocalizations. These effects are in some cases a simple depression or facilitation, but in many cases are more selective and complex. Whether these effects of serotonin are correlated with the location of the recorded neurons in the different IC subdivisions is unknown, since most of these recordings were made in the central subdivision. However, the serotonin effects do not correlate well with the depth of the recording electrode in the IC, or with neural response properties such as whether the neurons are transient versus sustained or monotonic versus non-monotonic (personal observations). Serotonin effects may be more extensive than has currently been reported, since serotonin effects on many aspects of auditory processing such as binaural integration or the effects of serotonin in different subregions of the IC have not yet been investigated.

5. Specificity

Relatively small numbers of serotonergic neurons innervate widespread regions of the brain and spinal cord, and even single serotonergic neurons may project broadly (Petrov et al., 1992; Allen and Cechetto, 1994; Kirifides et al., 2001; Li et al., 2001). Even though there is some specificity in the projections of different subgroups of serotonin neurons (for example Jacobs and Azmitia, 1992; Jacobs et al., 1978; Kirifides et al., 2001), the projections of serotonin neurons are likely to be fairly diffuse (Jacobs and Azmitia, 1992). For this reason, it is commonly assumed that serotonin effects are non-specific, and that serotonin will have only one type of effect on a given population of target neurons. The actual situation is quite different. Specificity of serotonin action exists at numerous different levels in the brain, and several of these have also been found in the auditory brainstem in general and the IC in particular.

One level of specificity is in the pattern of serotonergic fibers that project to the IC. As noted in a previous section, serotonergic fibers are not uniform in density across the IC. Fibers are most dense in the external regions of the nucleus, including the dorsal and external cortices (Hurley and Thompson, 2001; Kaiser and Covey, 1997; Klepper and Herbert, 1991), and are less dense, though still plentiful, in the central nucleus. Since different IC subdivisions contain different types of neurons (Morest and Oliver, 1984; Oliver and Morest, 1984), the anatomical evidence suggests that some neuron types receive more serotonergic input and therefore may be more subject to serotonergic modulation than others.

Further levels of specificity of serotonin modulation in the IC are suggested by electrophysiological experiments. These experiments reveal different kinds of specific serotonin effects. First, only about half of IC neurons recorded respond to exogenous serotonin application, while the remainder are unaffected. Thus, there are separate populations of affected and unaffected neurons. Second, the nature of serotonin effects is different in different groups of neurons which are modulated by serotonin; serotonin decreases the response to sound in the majority of neurons, but it increases the response to sound in other neurons. Finally and most interestingly, even within the range of responses of some single neurons, serotonin selectively affects the responses to certain sounds, such as tone bursts of a given frequency range, or a subset of species-specific vocalizations (discussed above). While the cellular mechanisms of these diverse effects of serotonin are not understood, these results are intriguing, and suggest that serotonin performs specific functional tasks in different populations of IC neurons. One major cav-

eat of this conclusion is that exogenously applied serotonin, which may not mimic endogenous patterns of serotonin release, was used in these experiments. Even so, such neuron-specific patterns of response suggest non-uniformity in the response to serotonin at some level.

Another level of specificity which has been extremely well-investigated in other regions of the brain, but hardly at all in the IC, is in the functions of different serotonin receptor subtypes and the corresponding intracellular cascades which they activate. Though four serotonin receptor types have been found in the IC, the functional consequences of having these different receptor types, and whether they mediate different effects of serotonin as measured electrophysiologically, are unclear.

Thus, although the pattern of projection of serotonin fibers to the IC may be diffuse, there are a number of anatomical and electrophysiological mechanisms which lead to specificity in the action of serotonin, both for single neurons and across the IC neuronal population.

6. Functions

A number of theories regarding serotonin function have been proposed based on the activity patterns of serotonergic neurons or the patterns of serotonin projections. Some of these theories potentially apply to or were developed in the auditory brainstem and midbrain. Here we consider whether recent electrophysiological data on the effects of exogenous serotonin on IC neurons are consistent with these theories, and what further functional consequences of serotonin are suggested by these electrophysiological data.

One of these theories addresses the role of behavioral state in the apparently opposite effects of serotonin on motor and sensory systems. Serotonin appears to strengthen or initiate the outputs in some motor systems, for example in locomotory networks (i.e. Jacobs and Fornal, 1993, 1999; Wallis, 1994; Sillar et al., 1998). Serotonin also inhibits some sensory inputs, such as nociceptive or somatosensory inputs, at a number of different levels, from the level of the brainstem and spinal cord (Jankowska et al., 1994, 1995; Lopez-Garcia, 1998) to the level of the cortex (Bassant et al., 1990; Eaton and Salt, 1989; Lopez-Garcia, 1998; Waterhouse et al., 1986). Some of the serotonergic neurons endogenously modulating these sensory and motor systems fire at higher rates during states of arousal than of non-arousal. Thus, in a state of heightened arousal, a proposed function of serotonin is to facilitate important motor outputs and to suppress non-essential sensory inputs. This has been called the motor hypothesis of serotonin function (Jacobs and Fornal, 1993). A consequence of this hypothesis is that serotonin should simply suppress the overall responsiveness of auditory neurons, including IC neurons.

In the IC, exogenously applied serotonin has been reported to depress the activity of neurons in response to sound (Faingold et al., 1991; Hurley and Pollak, 1999, 2001). As far as this goes, it supports the motor hypothesis of serotonin function. However, in some neurons, as noted above, serotonin effects are more complex than a simple gain control, since serotonin selectively depresses the responses to some sorts of sounds more than others (Hurley and Pollak, 2001). In these cases, even though serotonin depresses the responses to sounds, the end result is not a simple gain control but a change in the response range of the neurons. Moreover, in a minority of neurons, serotonin actually facilitates rather than depresses the responses to sounds. Thus, the predictions of the motor hypothesis apply for the neurons which are simply suppressed by serotonin, but not for the ones which are facilitated.

A second hypothesis regarding serotonin function in the IC grew out of patterns of serotonin staining in the auditory brainstem, and was proposed by Klepper and Herbert in 1991. The hypothesis is that serotonin strongly modulates regions which integrate inputs from auditory and non-auditory sources. Patterns of staining in the IC generally conform to this hypothesis. Serotonin fibers are denser in the dorsal and external cortices of the IC, and these regions also receive a somewhat different array of inputs than does the central IC. Like the central IC, the dorsal and external regions of the IC receive an array of inputs from lower auditory nuclei, though these inputs are reduced relative to the central nucleus (for example Oliver, 1987; Shneiderman et al., 1988; Oliver and Huerta, 1992). To a much greater degree than the central IC, the dorsal and external subdivisions of the IC also receive descending projections from the auditory cortex (for example Andersen et al., 1980; Luethke et al., 1989; Herbert et al., 1991; Winer et al., 1998). The non-central regions of the IC also receive projections from non-auditory regions, including visual regions (Itaya and Van Hoesen, 1982; Paloff et al., 1985; Hyde and Knudsen, 2000), somatosensory regions (Robards, 1979; Aitkin et al., 1981; Li and Mizuno, 1997), globus pallidus (Yasui et al., 1990; Moriizumi and Hattori, 1991; Shinonaga et al., 1992; Shammah-Lagnado et al., 1996), amygdala (Marsh et al., 1999), superior colliculus (Sato and Ohtsuka, 1996), and substantia nigra (Moriizumi et al., 1992), to name several. If the denser serotonin innervation in the non-central regions of the IC actually translates into larger serotonin effects in these regions, then serotonin could potentially alter the integration of the auditory and non-auditory inputs in these peripheral regions of the IC. For example, serotonin could differentially gate in-

puts from different sources, as it seems to do in the superior colliculus (Huang et al., 1993; Mooney et al., 1996). These are issues that remain to be explored.

A third hypothesis regarding serotonin function in the IC has emerged from our electrophysiological data. The hypothesis is a consequence of serotonin's tendency to have selective effects, in modulating only some neurons and in changing the selectivity of some neurons for auditory stimuli (Hurley and Pollak, 2001). If extrapolated across the population of IC neurons, these selective effects of serotonin would result in an altered pattern of activity for a given sound. The specific spatial and temporal patterns of activity in response to a sensory stimulus may be important for encoding that stimulus across a population of neurons (for example Binz et al., 1990; Stanley et al., 1999; Covey, 2000; Doetsch, 2000; Petersen and Diamond, 2000; Friedrich and Laurent, 2001; Tsunoda et al., 2001). Thus, serotonin, in selectively altering the responses of single IC neurons to existing inputs, could alter the patterns that encode particular sounds in the IC. Similar to the motor hypothesis, the most interesting feature of such an alteration is that it would be dependent on the level of arousal and on incoming sensory cues, since the activity of serotonergic neurons innervating the IC is also dependent on these variables. The firing of serotonergic neurons by a heightened state of arousal or by a novel stimulus could therefore induce a reconfiguration of the sound-processing circuitry of the IC, causing sounds to be encoded by more specific and limited patterns of activity. Whether such changes in activity pattern are triggered by endogenous sources of serotonin (see Section 7), and what sorts of behavioral consequences they entail are issues that are not yet understood.

These hypotheses are a limited sample of the possible functions that serotonin could perform in the IC. They are not mutually exclusive; indeed, given the massive convergence of inputs in the IC, and the range of functions which have been proposed for the IC (for examples, see Brandao et al., 1994; Covey and Casseday, 1999; Li et al., 1998a,b; Braun, 2000), it is not unreasonable to imagine that serotonin may be modulating multiple processes in the IC. Generating further ideas of serotonin function, as well as confirming or refuting existing ones, must rely on future electrophysiological, anatomical, and behavioral experiments.

7. Conclusions

There has long been substantial anatomical evidence for the modulation of IC neurons by serotonin. More recently, there has been mounting electrophysiological evidence that serotonin, as well as other neuromodulators (Faingold et al., 1991; Farley et al., 1983; Habbicht and Vater, 1996), can alter auditory processing in the IC. Thus, there is evidence that serotonin is in a position to modulate IC neurons, that exogenously applied serotonin does modulate IC neurons, and that the patterns of endogenous serotonin release are likely to be linked to behaviorally important internal cues and even to external sensory cues, including auditory stimuli.

Despite these growing findings, there are still a number of major issues related to serotonin in the IC which have not been investigated at all. One of these is the effect that endogenous sources of serotonin have in the IC. There are a number of reasons that endogenous sources of serotonin might not have the same effects as exogenously applied serotonin. One is that the concentration of exogenously applied serotonin could be higher or lower than the physiological range. A second is that the release of endogenous sources of serotonin is likely to be timed to behavioral events and thus coordinated with a background of other modulatory influences onto the IC. There is some evidence that different neuromodulatory systems can influence each other, at the level of the neuromodulatory neurons themselves (i.e. Couch, 1970; Koyama and Kayama, 1993) and also at the level of target cells (i.e. Canfield and Dunlap, 1984; Funke and Eysel, 1993). Looking at serotonin effects in isolation may therefore not replicate the in vivo situation. A third outstanding issue is that endogenous serotonin release is likely to be more widespread within the IC than exogenous application, given the distribution of release sites, and release would also not be limited to the IC. Serotonergic fibers innervate most lower nuclei of the auditory brainstem which project to the IC, and serotonin has been shown to have electrophysiological effects in some of these nuclei (Ebert and Ostwald, 1992; Fitzgerald and Sanes, 1999; Wang and Robertson, 1997). Thus, serotonin would probably modulate the activity of the inputs to the IC at the same time it modulates the activity of IC neurons themselves, potentially resulting in a different pattern of effects in the IC than that observed with local application of serotonin to the IC alone.

Overall, while many interesting and perhaps unexpected aspects of serotonin in the IC have been revealed to date, many new and exciting prospects, particularly regarding the links between serotonin effects and behavior, remain to be explored.

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