Review

Auditory gating processes and binaural inhibition in the inferior colliculus

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Abstract

Physiological/behavioral/perceptual responses to an auditory stimulus can be inhibited by another leading auditory stimulus at certain stimulus intervals, and have been considered useful models of auditory gating processes. Two typical examples of auditory gating are prepulse inhibition of the startle reflex and the precedence effect (echo suppression). This review summarizes studies of these two auditory gating processes with regard to their biological significance, cognitive modulation, binaural properties, and underlying neural mechanisms. Both prepulse inhibition and the precedence effect have gating functions of reducing the disruptive influence of the lagging sound, but prepulse inhibition has a much longer temporal window than the precedence effect. Attentional processes can modulate prepulse inhibition, and the listener's previous experience can modulate the precedence effect. Compared to monaural hearing, binaural hearing reduces prepulse inhibition but enhances the precedence effect. The inferior colliculus, the major structure of the auditory midbrain, plays an important role in mediating these two auditory gating processes, and inhibitory neural transmissions within the inferior colliculus may account for binaural inhibition observed in prepulse inhibition and lag suppression recorded in the inferior colliculus. The neural mechanisms underlying binaural inhibition in the inferior colliculus are also discussed.   © 2002 Elsevier Science B.V. All rights reserved.

Key words: Auditory gating; Prepulse inhibition; Precedence effect; Binaural inhibition; Inferior colliculus; Inhibitory transmission

1. Introduction

When a pair of clicks with a long interstimulus interval (ISI) (e.g., 500 ms) are presented to human subjects, the P50 component of the cortical evoked potential elicited by the second click is normally suppressed compared to the P50 elicited by the first click. The suppression effect indicates an inhibitory sensory gating process, and is called 'P50 gating' (for a recent review see Light and Braff, 1998). If the concept of sensory gating is generalized to the reduction of all consequences of the lagging stimulus, the indices of sensory gating should include reduction of both overt behavioral and perceptual responses to sensory stimulation, in addition to changes in the amplitude of event-related potentials and other physiological indices.

A sudden and intense acoustic stimulus can elicit the startle reflex, which, however, can be suppressed by a weak sound that is presented 10–500 ms before the startling sound. This phenomenon has been referred to as acoustic prepulse inhibition (PPI) and is considered a model of sensorimotor gating (Braff and Geyer, 1990; Graham, 1975; Hoffman and Ison, 1980; Ison and Hoffman, 1983). On the other hand, the precedence effect (PE), which was first proposed by Wallach et al.

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Abbreviations: DNLL, dorsal nucleus of the lateral lemniscus; EI, excitatory (contralateral)/inhibitory (ipsilateral); GABA, γ-aminobutyric acid; IC, inferior colliculus; IE, inhibitory (contralateral)/excitatory (ipsilateral); IID, interaural intensity difference; ISI, interstimulus interval; ITD, interaural time difference; LSO, lateral superior olivary nucleus; PE, precedence effect; PnC, caudal pontine reticular nucleus; PPI, prepulse inhibition; PPTg, pedunculopontine tegmental nucleus; SC, superior colliculus; SOC, superior olivary complex

(1949), has been defined based on subjective impression related to echo suppression. In a reverberant environment, a sound propagates to the ear directly and is followed by its reflections from many other directions. The reflections, therefore, would compete with the original sound for perception and localization. However, listeners can normally perceive and localize the original sound correctly with little influence from the reflected sounds, indicating an effect of echo suppression induced by the original sound. PE contains a group of phenomena, including fusion, localization dominance and lag discrimination suppression (for a recent review see Litovsky et al., 1999). These phenomena reflect the interaction between an original sound (leading sound) and its reflections (lagging sounds) for perception and localization.

This paper provides a comprehensive review of studies of PPI and PE, summarizing similarities and differences between PPI and PE in their biological significance, cognitive modulation, binaural integration and underlying mechanisms.

2. Functions of auditory gating and protection-of- processing theory

2.1. Prepulse inhibition

The startle reflex has a strong disruptive effect on ongoing cognition and behavioral execution (Foss et al., 1989; Hoffman and Overman, 1971). PPI of the startle reflex occurs across mammalian species studied at a variety of postnatal ages, thus it must have an important function for mammals. According to Graham's (1975) protection-of-processing theory for explaining PPI, the onset of low-intensity changes in sensory stimulation produces a 'transient detection reaction' that automatically triggers a gating mechanism attenuating responses to startling stimuli temporarily until the perceptual processing of the leading stimulus is completed. This theory is supported by evidence that perception of the prepulse sound becomes more accurate when it produces more inhibition of startle (Filion and Ciranni, 1994; Mussat-Whitlow and Blumenthal, 1997; Norris and Blumenthal, 1995, 1996; Perlstein et al., 1989, 1993). Also, the startling sound is perceived as less intense when it is preceded by a prepulse sound (Blumenthal et al., 1996; Perlstein et al., 1993).

PPI can be induced by any acoustic events regardless of the signal correlation between the prepulse and the startling stimuli. For example, acoustic prepulse stimuli can be noise, pure tones, and even a brief silent period (gap) in continuous noise (Ison and Pinckney, 1983). Also, PPI of the pinna startle reflex does not exhibit azimuthal directional sensitivity (Li and Frost, 2000). Therefore, acoustic PPI is a type of non-selective sensory gating.

Since inhibition of startle can occur shortly (less than 50 ms) after the appearance of the prepulse stimulus and does so on the first trial, PPI reflects neither voluntary behavioral inhibition nor learning.

2.2. The precedence effect

The protection-of-processing theory can also extend to echo suppression. When the interval between the leading and the lagging sound is less than 10 ms, only one sound is heard and the perception is called 'fused'. The fusion effect may be useful for preventing multiple sound images arising from both a sound source and its reflections. In addition to fusion, the perception of location of the fused sound is dominated by the leading sound location. For example, Litovsky (1997) reported that at short lead/lag delays (1, 2 and 4 ms), the fused sound was perceived as from the leading speaker on a majority of trials when the two free-field speakers were placed in the azimuthal plane (one at the midline and the other at 30° right). This phenomenon is so-called localization dominance and indicates that the auditory system assigns much greater perceptual weight in sound localization to the leading sound than to the lagging sounds in echoic environments.

It is well known that the auditory system largely depends on binaural cues to localize sounds. The two important binaural cues are interaural time difference (ITD) and interaural intensity difference (IID). When sounds are delivered with headphones, the leading sound reduces the listener's ability to discriminate changes in ITDs or IIDs of the lagging sound (Gaskell, 1983; Tollin and Henning, 1998; Zurek, 1980), indicating a temporary loss of sensitivity to the binaural cues shortly after the onset of the leading sound (Zurek, 1980). This echo suppression effect of the leading sound on spatial sensitivity to the lagging sound, so-called lag discrimination suppression, can also be demonstrated in free-field experiments. When the leading and lagging sounds are perceived fused, the minimum audible angle for detecting location change of the lagging sound is larger than when the same lagging sound is presented alone (Litovsky, 1997; Litovsky and Macmillan, 1994; Perrott et al., 1987, 1989; Perrott and Pacheco, 1989).

Harris et al. (1963) proposed the gating concept of echo suppression. They speculated that the neural gate related to binaural processing would close about 1 ms after the first neural response, and then reopen 2 or slightly more ms later. Therefore, the temporal window of precedence would last for a few ms for clicks, "permitting no further neural timing signals to be sent to the brain."

The amount of PE largely depends on the spectral similarity between the leading and lagging sounds. For example, fusion is stronger when the leading and lagging noises are highly correlated while it is weaker when the leading and lagging noises contain uncorrelated spectral components (Perrott et al., 1987). In addition, lag discrimination suppression increases as the spectral overlap between the leading and lagging sounds is increased (Blauert and Divenyi, 1988). This feature of PE is important for segregation of acoustic events in an echoic environment.

It is well known that spatial separation of the source of speech from the source of interference can improve the perception of speech. The studies by Freyman et al. (1999, 2001) have shown that when a target nonsense speech and an interference nonsense speech are played from the same speaker at the same time, subjects have more difficulty in recognizing the target speech. However, when localization dominance of PE is introduced by two spatially separated speakers, subjects feel that the target speech and the interference speech seem to come from different speakers, even though each speaker delivers both target and interference speeches. The subjectively perceived spatial separation of the target and interference speeches improves the recognition of the target speech. Therefore, a high order of cognitive processing is involved in PE.

2.3. Comparison between prepulse inhibition and the precedence effect

Both PPI and PE reflect information-protective mechanisms of the auditory system. These mechanisms attribute relatively greater perceptual weight to the first-arriving sound and inhibit physiological/behavioral/perceptual responses to the lagging sound within a certain temporal window, and therefore, minimize confusion and interruptions that are produced by lagging stimuli. Although PPI and PE have similar gating functions, they have obvious differences. First, PPI is measured directly with the change in startle amplitudes, without reflecting any voluntary performance, and thus can be observed in a similar way throughout mammal species; PE, however, is estimated from perceptual discrimination responses in humans and animals. In addition, the inhibitory effect of the prepulse stimulus on startle can last from 10 to 500 ms, which is much longer than the temporal window for PE as measured with echo threshold. Finally, PPI does not depend on the signal similarity between prepulse and startling stimuli, but PE largely depends on the spectral correlation between leading and lagging stimuli. Thus PPI is a type of non-information-selective sensory gating, and PE is a type of strictly information-selective sensory gating.

3. Cognitive modulation of auditory gating

3.1. Prepulse inhibition

PPI can be observed in decerebrate rats (Davis and Gendelman, 1977; Fox, 1979; Li and Frost, 2000), and it has been considered to reflect the action of automatic processes (Graham, 1975). However, studies in humans have indicated that PPI can be modulated by controlled attentional processes: PPI is greater when subjects are attending to the prepulse sounds than when the prepulse sounds are ignored (Acodella and Blumenthal, 1990; Hackley and Graham, 1987; Filion et al., 1993). Interestingly, attentional modulation of PPI occurs only at certain ISIs (e.g., 120 ms, Filion et al., 1993). PPI, therefore, represents not only the automatic protective processes of sensorimotor gating, but also the early stages of controlled attentional processes.

Over the past years, studies of PPI have received considerable attention, because it has been found that deficits of PPI have a close link with some psychiatric disorders, such as schizophrenia (for a recent review see Braff et al., 2001). Hence the interplay between PPI and cognition is no doubt a critical issue of the future investigation.

3.2. The precedence effect

Listeners' previous short-term experience during repeated presentation of the leading and lagging stimuli can enhance or reduce the PE. As the ISI between leading and lagging sounds is increased to above the echo threshold, the lagging sound becomes perceived as a separate acoustic event at its own location. If a leading–lagging paired click stimulus is presented repeatedly several times, the echo threshold for the last leading–lagging pair is raised by a few ms, indicating that PE is facilitated (Clifton and Freyman, 1989; Freyman et al., 1991; Thurlow and Parks, 1961; Yang and Grantham, 1997; Yost and Guzman, 1996). This phenomenon, called buildup of precedence, suggests that some sort of adaptation is introduced following repetitions of stimulation so that listeners become less sensitive to reflections (Litovsky et al., 2000). Interestingly, buildup of fusion, localization dominance or lag discrimination suppression can be interrupted by changing some parameters of the leading and lagging sounds. For example, if the locations of the leading and lagging sounds suddenly switch (the leading sound occurs where the lagging sound had been and vice versa), buildup of precedence is interrupted (Clifton, 1987). Interruption of buildup can also be introduced by violating listeners' expectations about the lead/lag delay. For example, when the interval of the last pair of leading and lagging

noise pulses are different from those of previous ones in a train, the echo threshold of the last pair is lower, compared to trials when there is no change between the last and the previous pairs (Clifton et al., 1994). The interruption of buildup is often called a 'breakdown' or 'release from suppression'. Both buildup and breakdown of precedence phenomena suggest that higher centers of the brain are involved in modulation of PE, and that when unexpected interruptions are not compatible with listeners' previous short-term experience, the mechanisms regulating the processes of repeated lead–lag events would be reorganized. Clifton et al. (1994) proposed that reflections are useful in providing information about a listener's acoustic environment and helping the listener form 'expectations' about the sounds that can occur next. If the features of a sound are not compatible with the expected acoustic environments, fusion and/or lag discrimination suppression breaks down.

3.3. Comparison between prepulse inhibition and precedence effect

Attentional processes play a role in modulating PPI. PPI has been described as showing no habituation or adaptation (e.g., Wu et al., 1984), but PE can be enhanced by repeated presentation of the leading–lagging click pair. Both the 'buildup' and the 'breakdown' effects imply that PE is influenced by the listener's previous experience. It is of interest to know whether the 'buildup' and 'breakdown' effects also reflect the two opposite modulations of attentional processes.

Knowledge about modulation of PPI is important not only for expanding our understanding of the basic brain functions, but also for discovering pathophysiology of some psychiatric disorders, such as schizophrenia, which are characterized by PPI deficits (for a recent review on neural modulation of PPI, see Swerdlow et al., 2001). Since PE is also a type of sensory gating, which shares similar protective functions with PPI and has an even closer relationship with cognitive processing, it is more interesting and important to study PE deficits that may be associated with certain populations, such as those with psychiatric disorders.

4. Binaural integration

4.1. Prepulse inhibition

The strength of PPI depends on the energy of the prepulse sound delivered to the ears. As the intensity of the prepulse sound is increased, the strength of prepulse inhibition is likewise enhanced (Hoffman and Ison, 1980; Li et al., 1998a). However, inhibition of

the eyeblink reflex is greater when the prepulse sound is delivered to one ear than when delivered to two ears (Hoffman and Stitt, 1980; Hoffman et al., 1981; Ison and Pinckney, 1990; Marsh et al., 1976; Stitt et al., 1980). Also, binaural acoustic stimulation with large disparities in either ITD or IID is more effective in inhibiting the eyeblink reflex than that with small disparities (Hoffman and Stitt, 1980; Ison and Pinckney, 1990). Thus it has been speculated that the monaural–binaural effects of prepulse stimuli on the eyeblink reflex may be mediated via the neural pathways that convey and compare excitatory inputs to the auditory brainstem from one ear and inhibitory inputs from the other ear (Hoffman and Stitt, 1980; Ison and Pinckney, 1990). In other words, binaural inhibition is involved in PPI.

4.2. The precedence effect

PE is defined by the dominant effect of the leading sound in determining the location of the acoustic image and the reduced spatial contribution of the lagging sound. In fact, PE does not consist of a general suppression or attenuation of the lagging sound but suppression that is limited to directionality cues (Freyman et al., 1998). Obviously, binaural processing is involved in PE, in particular, within the azimuthal plane (Litovsky et al., 1997). Although PE can be experienced with monaural hearing, it is greatly enhanced with binaural hearing. For example, echo suppression is more effective in the azimuthal plane than in the median plane (Rakerd and Hartmann, 1992), and precedence is mediated by binaurally based and spectrally based localization cues in the azimuthal and sagittal planes, respectively. Monaural deafness causes confusion in localizing paired sounds (Hochster and Kelly, 1981). Unlike PPI, which is weakened by binaural hearing, PE is enhanced by binaural hearing. Studies of the physiological correlates of the PE have suggested that binaural inhibition in the IC is likely the critical substrate underlying the PE (see below).

5. Neural bases of prepulse inhibition and echo suppression

5.1. Prepulse inhibition

PPI can be detected in decerebrate rats (Davis and Gendelman, 1977; Fox, 1979; Li and Frost, 2000), indicating that the primary pathways mediating PPI are located in the brainstem. The auditory midbrain, the inferior colliculus (IC), occupies a critical position in the auditory system for acoustic information processing. Several studies have indicated that the IC mediates
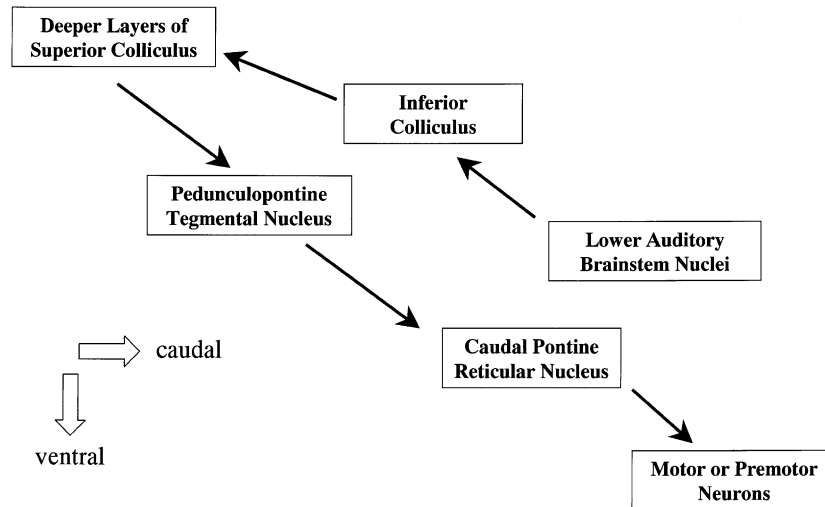
Fig. 1. Schematic diagram showing the neural pathway mediating acoustic prepulse inhibition.

acoustic PPI. First, large bilateral radio-frequency destruction of the IC and surrounding areas eliminates acoustic PPI (Leitner and Cohen, 1985). In addition, restricted unilateral excitotoxic lesions of the IC reduce acoustic PPI without changing the baseline startle (Li et al., 1998a). Finally, unilateral electrical stimulation of the IC before an acoustic startling stimulus mimics the inhibitory effect of an acoustic prepulse sound, with the optimal ISI at 15–30 ms (Li et al., 1998b). Therefore, the IC can be considered the first relay station in the pathway mediating acoustic PPI.

How are PPI signals transferred to the startle pathway from the IC? In mammals, the IC sends vast axonal projections to the deeper layers of the superior colliculus (SC) from various subdivisions, including the dorsomedial region, the external nucleus, and the nucleus of the brachium of the IC (Appell and Behan, 1990; Cadusseau and Roger, 1985; Covey et al., 1987; Druga and Syka, 1984; Hashikama and Kawamura, 1983; Kudo et al., 1984; Lugo-Garcia and Kicliter, 1988; Saint Marie, 1996; Thiele et al., 1996; Van Buskirk, 1983; Wallace and Fredens, 1989; Zhang et al., 1987). The SC is an important midbrain structure processing multi-modal information (Meredith et al., 1992; Sparks, 1986), and plays a role in mediating PPI (Fendt, 1999; Fendt et al., 1994; Li and Yeomans, 2000). In addition to acoustic stimuli, PPI can be produced using either tactile or visual sensory inputs (Buckland et al., 1969; Pickney, 1976). The SC may therefore be involved in mediating multi-modal PPI. The SC projects to the pedunculopontine tegmental nucleus (PPTg) (Redgrave et al., 1987; Semba and Fibiger, 1992; Steiniger et al., 1992), which is another important structure mediating PPI (Koch et al., 1993; Kodsi and Swerdlow, 1997; Swerdlow and Geyer, 1993). The PPTg, in turn, projects bilaterally to the

caudal pontine reticular nucleus (PnC) (Koch et al., 1993), an obligatory relay station in the primary startle pathway for integrating prepulse and startling signals (for recent reviews see Koch and Schnitzler, 1997; Lee et al., 1996; Yeomans and Frankland, 1996). Fig. 1 summarizes the proposed pathway mediating acoustic PPI. Some studies have suggested that the long-lasting effect of PPI may be mediated by both muscarinic acetylcholine receptors and γ-aminobutyric acid-B ($GABA_B$) receptors in the PnC (Fendt and Koch, 1999; Koch et al., 1993, 2000).

5.2. The precedence effect

To date the neural substrates underlying the PE are not well known. Since the IC occupies a critical relay station in both ascending and descending auditory pathways, it has received considerable attention in studies on physiological correlates of PE. Most IC neurons, under both dichotic and free-field conditions, exhibit suppressed responses to the lagging click when the leading click is presented over a large range of ISIs (Carney and Yin, 1989; Fitzpatrick et al., 1995; Kidd and Kelly, 1996; Litovsky, 1998; Litovsky and Yin, 1998a,b; Litovsky et al., 1997; Yin, 1994). This suppression effect is obvious even if the leading click is less intense and does not elicit a response in the IC (Carney and Yin, 1989). These data lead to the speculation that the inhibitory effect of the leading sound on the neural responses in the IC to the lagging sound may be part of the neural basis of echo suppression.

Fitzpatrick et al. (1995) reported that half of their sampled neurons from the unanesthetized rabbit's IC showed stronger lag suppression when the ITD of the leading sound was near the 'best' ITD, while the other half of the neurons showed stronger suppression when

the ITD was near the 'worst' ITD. Litovsky and Yin (1998b) reported that the majority of their sampled neurons from the anesthetized cat's IC exhibited stronger lag suppression when the leading sound was presented in the field locations that were most excitatory for the neuron or when the leading sound was set at a favorable ITD for the neuron. These data indicate that the inhibitory sources themselves, which elicit lag suppression in the IC directly, are sensitive to stimulus location or ITD, and therefore that the monaural auditory nuclei are less involved directly in the mediation of lag suppression in the IC. Thus, the essential investigation of the neural mechanisms underlying lag suppression in the IC is to find out the physiological functions of those binaural auditory structures that send inhibitory projections to the IC. As suggested by several research groups (Burger and Pollak, 2001; Fitzpatrick et al., 1995; Kidd and Kelly, 1996; Litovsky and Yin, 1998b; Yin, 1994), the structure in the auditory brainstem important to lag suppression in the IC is the dorsal nucleus of the lateral lemniscus (DNLL).

The durations of suppression of neural responses recorded in the IC to the lagging sound are longer than those in the lower auditory brainstem structures, but shorter than those in the auditory cortex (Fitzpatrick et al., 1995, 1999). Therefore, echo suppression may need action of the higher auditory system, including the auditory cortex. Indeed, both human and animal studies have confirmed that PE is regulated by the cortex. Damage to the temporal lobe or auditory cortex causes deficits in PE-related sound localization performance (Cornelisse and Kelly, 1987; Cranford et al., 1971; Hochster and Kelly, 1981; Whitfield et al., 1978). Using a mathematical method to isolate the auditory evoked potentials to the lagging sound in humans, Liebenthal and Pratt (1999) provided electrophysiological evidence for involvement of the primary auditory cortex in the PE when the leading and lagging sounds were delivered binaurally.

6. Mechanisms underlying binaural inhibition in the inferior colliculus

If the IC–SC–PPTg–PnC chain connection is important for mediating PPI, some response features of any link in this chain connection, such as binaural integration in the IC, may be reflected in PPI. As mentioned before, binaural inhibition is involved in PPI (Hoffman and Stitt, 1980; Hoffman et al., 1981; Ison and Pinckney, 1990; Marsh et al., 1976; Stitt et al., 1980), and the involvement of binaural inhibition in PPI, accordingly, could be used as a behavioral index of binaural processing in the IC. On the other hand, binaural integration enhances PE (Liebenthal and Pratt, 1999; Rakerd and

Hartmann, 1992). The azimuthal cues that determine PE are bilaterally based, and the amount of lag suppression observed from the IC is also determined by the location of the leading sound in a free field (Litovsky, 1998; Litovsky and Yin, 1998b; Litovsky et al., 1997). Yin (1994) argued that long-lasting suppression detected in the IC does not reflect a long-lasting intrinsic refractory period, but is due to synaptic inhibition. As mentioned above, it has been proposed that GABAergic projections from the DNLL to the IC may play a major role in mediating lag suppression recorded from the IC (Burger and Pollak, 2001; Fitzpatrick et al., 1995; Kidd and Kelly, 1996; Litovsky and Yin, 1998b; Yin, 1994). Actually, the inhibitory DNLL projections to the IC indeed play an important role in shaping binaural inhibitory responses in the IC (see below).

Undoubtedly, binaural processing, particularly binaural inhibitory processing in the IC, is important to PPI and PE. The mammalian IC contains a large number of so-called binaural excitatory–inhibitory (EI) neurons that are predominately excited by sound at the contralateral ear and inhibited by sound at the ipsilateral ear, showing binaural inhibitory responses (for a review see Irvine, 1986). It was assumed that binaural sensitivity in the IC might be a direct reflection of binaural interactions occurring at lower levels of the auditory brainstem, particularly in the superior olivary complex (SOC) (Irvine, 1986, p. 161). For example, the majority of neurons in the lateral superior olivary nucleus (LSO) receive 'IE' binaural inputs (i.e., contralateral inhibition and ipsilateral excitation) (Boudeau and Tsuchitani, 1968; Caird and Klinke, 1983; Tsuchitani and Boudreau, 1969). The response of IE cells of the LSO is maximal when the stimulus at the ipsilateral ear is more intense (corresponding to ipsilateral azimuths), and is suppressed when the stimulus at the contralateral ear is more intense (corresponding to contralateral azimuths). In a number of mammalian species, bilateral projections of the LSO to the IC have been identified (Adams, 1979; Brunso-Bechtold et al., 1981; Elverland, 1978; Glendenning and Masterton, 1983; Henkel and Brunso-Bechtold, 1993; Beyerl, 1978; Coleman and Clerici, 1987; Zook and Casseday, 1982). If projections from IE neurons in the LSO to the contralateral IC are excitatory in nature, the laterality of binaural responses of their target neurons in the contralateral IC would be reversed to EI. The sign EI indicates that stimulation to the contralateral ear is predominantly excitatory and stimulation to the ipsilateral ear is predominantly inhibitory. In fact, the IID sensitivity functions of IE neurons in the LSO are generally mirror symmetric with those of EI cells in the contralateral IC.

Nevertheless, large chemical lesions of the SOC did not eliminate the EI response in the IC (Li and Kelly,

1992a; Sally and Kelly, 1992), indicating that binaural inhibition in the IC cannot be explained exclusively by a direct reflection of the IE response in the SOC. In fact, it has become evident that binaural inhibitory processing that occurs in the IC is partially determined by inhibitory transmissions within the IC. For example, in vivo intracellular recordings from neurons in the IC have shown that stimulation of the contralateral ear can elicit excitatory postsynaptic potentials and stimulation of the ipsilateral ear can elicit inhibitory postsynaptic potentials (Kuwada et al., 1997; Pedemonte et al., 1997; Torterolo et al., 1995), indicating that one of the neural bases underlying EI responses of IC neurons is the local excitatory/inhibitory postsynaptic interaction driven by binaural stimulation.

Considerable data have further indicated that the inhibitory amino acids GABA and glycine function as the chemical mediators of binaural inhibition in the IC. The GABA-immunoreactive nerve terminals that form symmetric synapses contain flattened or pleomorphic vesicles and cover the cell bodies and dendrites of the large neurons of the IC (Ribak and Roberts, 1986). Calcium-dependent, potassium-evoked release of GABA from IC slices has been reported (Lopez-Colome et al., 1978). For the postsynaptic component, high levels of GABA$_A$ receptor and benzodiazepine receptor binding have been observed in the IC (Bristow and Martin, 1988; Glendenning and Baker, 1988; Seighart, 1986). IC neurons are also strongly labeled for the mRNA that encodes the α-1 subunit of the GABA$_A$ receptor (Hironaka et al., 1990). On the other hand, calcium-dependent, potassium-evoked release of glycine from IC slices has been reported (Lopez-Colome et al., 1978), and receptor binding for glycine and strychnine has also been detected in the IC (Araki et al., 1988; Glendenning and Baker, 1988; Probst et al., 1986; Sanes et al., 1987; Zarbin et al., 1981). Binaural responses in the IC can be altered by local application of antagonists of GABA or antagonists of glycine. For example, local injection of either the GABA$_A$ antagonist bicuculline or the glycine antagonist strychnine into the IC reduced the extent of binaural suppression of EI responses in IC of both rats (Faingold et al., 1989, 1991) and mustache bats (Park and Pollak, 1993).

Several lines of evidence suggest that the DNLL plays a critical role in shaping binaural inhibitory responses in the IC. First, most neurons in the DNLL are GABAergic (Adams and Mugnaini, 1984; Glendenning and Baker, 1988; Moore and Moore, 1987; Roberts and Ribak, 1987; Thompson et al., 1985). A subpopulation of these GABAergic neurons in the DNLL project to the IC (Gonzalez et al., 1996; Zhang et al., 1998), and the axonal terminals in the IC contain pleomorphic synaptic vesicles usually associated with inhibitory func-

tion (Oliver and Shneiderman, 1989; Shneiderman and Oliver, 1989). In addition, following ablation of the DNLL of the guinea pig, GABA release from IC was depressed in direct proportion to the degree of neuronal loss in the lesioned DNLL (Shneiderman et al., 1993). After complete unilateral ablation of the DNLL, GABA release in the contra- and ipsilateral IC was reduced by 51% and 25% respectively. Finally, chemical blockade of the DNLL reduced the strength of binaural inhibition in the contralateral IC but not in the ipsilateral IC (Burger and Pollak, 2001; Faingold et al., 1993; Kelly and Kidd, 2000; Kelly and Li, 1997; Kidd and Kelly, 1996; Li and Kelly, 1992b).

The DNLL is one of the binaural nuclei in the auditory brainstem. It has been confirmed that the majority of binaural DNLL cells sampled from several mammalian species are EI cells (Aitkin et al., 1970; Brugge et al., 1970; Covey, 1993; Kelly et al., 1998; Markovitz and Pollak, 1994). These cells are predominantly excited by contralateral stimulation and inhibited by ipsilateral stimulation. Therefore, the inhibitory influence of the DNLL to the IC is largely binaural in nature.

However, it must be pointed out that the DNLL is not the only auditory brainstem structure determining binaural inhibition in the IC. After kainic acid lesions of the DNLL, EI responses in the IC could still be detected (Li and Kelly, 1992c). There must be other lower auditory brainstem structures that play a significant role in determining binaural inhibitory responses in the IC, such as the contralateral LSO that contains a large number of binaural inhibitory neurons and sends excitatory projections to the IC. It is important to investigate this crossed excitatory influence from LSO neurons. Additional extrinsic inhibitory axonal projections to the IC come from the ipsilateral LSO. A large proportion of LSO principal neurons are glycine-immunoreactive and project to the ipsilateral IC directly (Aoki et al., 1988; Saint Marie and Baker, 1990; Saint Marie et al., 1989; Wenthold et al., 1987). Saint Marie et al. (1989) suggested that the ipsilateral inhibitory projection to the IC from the glycinergic LSO neurons may contribute to binaural inhibition in the IC. To examine this view, Kelly and Li (1997) studied the effect of blocking the ipsilateral SOC on binaural inhibition in the IC. Following injection of kynurenic acid into the ipsilateral SOC, marked reduction of binaural inhibition was observed in the rats with surgical transection of the contralateral lateral lemniscus at a level just below the DNLL.

Therefore, both the contralateral DNLL and the ipsilateral SOC make important contributions to binaural inhibition in IC, but neither the SOC nor the DNLL is essential alone. The convergent physiological functions of inhibitory inputs from the contralateral DNLL and the ipsilateral SOC to the IC in determining auditory

gating remain an important subject for further investigations.

Previous data have suggested that a similarity between PPI and PE in their underlying mechanisms is that binaural inhibition in the IC is involved in these two auditory gating processes. Neural inhibitory transmissions in the IC, which are associated with binaural processing, may regulate the two auditory sensory gating processes. Furthermore, the time courses of the inhibitory influences from the DNLL and SOC to the IC may affect the time courses of PE and PPI. For example, both DNLL and LSO neurons contain the two types of glutamate receptors: non-NMDA and NMDA receptors, which mediate fast and slow excitatory neural activity, respectively (Wu and Fu, 1998; Wu and Kelly, 1996). As suggested by Kelly and Kidd (2000), one of the functional contributions of NMDA receptors in the DNLL might be to extend the period of excitation in the DNLL and thus prolong the period of inhibition in the IC, providing a neural mechanism for echo suppression. Since the LSO also contains both non-NMDA and NMDA glutamate receptors (Caicedo and Eybalin, 1999; Sato et al., 1999; Wu and Fu, 1998; Wu and Kelly, 1992, 1996), it is of interest to know whether Kelly and Kidd's suggestion can extend to the contribution of NMDA receptors in certain LSO neurons. Certainly further in vivo studies are needed to address this issue.

7. Conclusion

Acoustic PPI and PE are two important sensory gating processes in the auditory system. They are important for both humans and animals to protect processing of auditory perception against disruption from lagging sounds within a temporal window. Compared to PPI, PE has higher temporal resolution and higher informational selectivity. PPI can be modulated by attentional processes, and PE can be modulated by immediate hearing experience, indicating that higher brain levels can regulate the two auditory gating processes. Since binaural integrations are involved in both PPI and PE, and the IC mediates both PPI and PE, binaural processing within the IC is one of the major mechanisms underlying auditory gating processes. Inhibitory axonal projections from the contralateral DNLL and the ipsilateral SOC to the IC determine the binaural inhibitory responses of EI neurons in the IC.

Acknowledgements

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