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REVIEW

Neural modulation in inferior colliculus and central auditory plasticity

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Abstract The neural modulation in central auditory system plays an important role in perception and processing of sound signal and auditory cognition. The inferior colliculus (IC) is both a relay station in central auditory pathway and a sub-cortical auditory center doing the sound signal processing. IC is also modulated by the descending projections from the cortex and auditory thalamus, medial geniculate body, and these neural modulations not only can affect ongoing sound signal processing but can also induce plastic changes in IC.

Keywords neural modulation, auditory plasticity, inferior colliculus

1 Introduction

The neural modulation in central auditory system plays an important role in maintaining the diversity and accuracy of neural functions. All sound signals of audible frequency can be heard or perceived by ear; however, we only notice the sounds that we are interested in, and other sound signals that assumed to have no biologic significance are filtered during transmission upward to different auditory centers. It is the various neural modulations that contribute to the filtration. Otherwise inferior colliculus (IC), which is divided basically into three parts of central nucleus (ICc), external nucleus (ICx) and dorsal nucleus (ICd) (Stiebler and Ehret, 1985), as a relay station in central auditory pathway, on one hand, receives the ascending excitatory and inhibitory inputs from lower auditory centers and projects to higher auditory centers; on the other hand, it receives the descending excitatory and inhibitory inputs from higher auditory centers and becomes an important part where descending modulation works. It is believed that a mechanism of promoting auditory sensitivity is that the higher auditory center sends out the modulation in response to sound signal inputs from the lower center. As a subcortical auditory center, IC is also involved in analysis and integration of sound signals in terms of amplitude, frequency and time course, etc.

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2 The neural modulation of descending projection to IC

2.1 Corticofugal control system from auditory cortex to IC

There are anatomical and morphological evidences that the descending fibers from the primary auditory cortex (AC or AI) terminate in ICc (Feliciano et al., 1995), ICx and ICd (Feliciano and Potashner, 1995) (Fig. 1a). At present, many researchers have discussed the modulation from AC to IC at cell level by means of electrically stimulating the local AC and activating the descending fibers directly. The effects of neural modulation which was called the corticofugal control of auditory sensitivity are various. For example, it was reported that the corticofugal control system affected auditory sensitivity in the bat IC (Sun et al., 1989; Sun et al., 1996; Zhang and Suga, 1997; Zhang et al., 1997; Jen et al., 1998; Yan and Suga, 1998), compressed all types of rate-intensity functions (Zhou and Jen, 2000a), changed amplitude domain and frequency information processing of IC neurons in the big brown bat (Zhang et al., 1997; Jen and Zhou, 2003), shaped frequency tuning and directional sensitivity of IC neurons in the mouse (Yan et al., 2005; Han et al., 2008), modulated the spectrotemporal patterns of responses, time-domain, and duration tuning of IC neurons in bats (Yan and Suga, 1996; Ma and Suga, 2001a; Ma and Suga, 2008). Moreover, excitatory or inhibitory postsynaptic potential (EPSP or IPSP) was directly recorded after electrically

stimulating the local AC in cats (Mitani et al., 1983). In these previous studies, the descending modulation from AC to IC seems to play an important role in acoustic information processing, and the corticofugal modulation works through different ways. Besides the way of direct projection from AC to IC, a descending polysynaptic pathway of AC–ICx–ICc was found when AC was electrically stimulated, and the auditory responses in ICc and ICx were recorded simultaneously (Jen et al., 2001). That is to say, some IC neurons being inhibited by corticofugal modulation are resulted from the corticofugal facilitation of ICx neurons and inhibition of ICx neurons to ICc neurons (Fig. 1b).

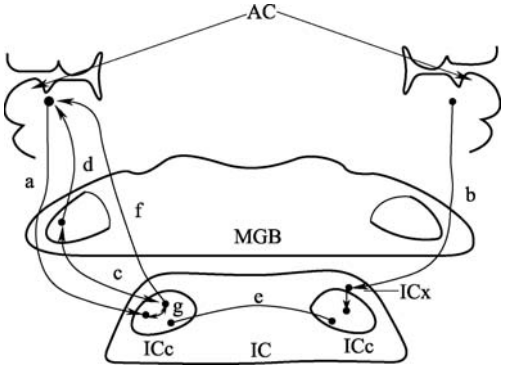

Fig. 1 Neural modulatory pathways to IC (redrawn according to Wang and Wang, 2005). a: direct projection from AC to IC; b: polysynaptic pathway of AC–ICx–ICc; c: connection from medial geniculate body (MGB) to IC; d: connection from MGB to AC; e: CoIC between two ICs; f: connection from IC to AC; g: connection between two neurons in one IC; c–d–a: IC–MGB–AC–IC feedback loop; f–a–g: IC–AC–IC corticofugal system.

2.2 The neural modulation from medial geniculate body to IC

As a higher subcortical auditory center, the medial geniculate body (MGB) relays ascending information from IC to the cortex, and also projects some descending fibers to IC. Electrically stimulating MGB could lead to shifts of IC neuron responses, which are similar to the shifts of IC neuron responses induced by electrically stimulating AC. For instance, the receptive fields (RFs) of IC neurons shifted toward stimulated MGB neurons' RF (Wu and Yan, 2007). Is this kind of modulation was induced completely by the inputs from MGB to IC? Later on, Wu and Yan (2007) found that electrically stimulating MGB did not induce any significant modulations in collicular neurons when AC was inactivated by muscimol, an agonist of γ-aminobutyric acidergic (GABAergic) A receptor. While in another study, multiparametric shifts in RF of auditory cortical neurons were induced toward activated thalamic auditory neurons by electric stimulation (Jafari et al., 2006). Therefore, it is supposed that electric stimulation of MGB may modulate IC neuron responses to sound stimulus through a feedback loop between AC and IC (IC–MGB–AC–IC), which has been anatomically proved to link the IC, MGB and AC in a tonotopic loop (Fig. 1c–d–a). However, certain parameters of the RFs of individual collicular neurons still showed some random changes after inactivation of AC; thus we cannot exclude the possibility of thalamocollicular modulation. The function of projections from MGB to IC remains to be further studied.

3 The neural modulation and interaction between two ICs

Since ICs are paired auditory structures in midbrain, there quite possibly are interactions between two ICs which participate in processing and integration of acoustic information as well as neural modulation. A previous study has demonstrated that there is commissure of the inferior colliculus (CoIC) between two ICs (Saldana and Merchan, 1992) (Fig. 1e) and the CoIC fibers interconnect mirror symmetric regions of the ICs representing similar frequency laminas (Malmierca et al., 1995). A study of intracellular recording on gerbil IC neurons *in vitro* has indicated that there are EPSP and IPSP evoked by direct stimulation of CoIC (Moore et al., 1998), also the existence of glutamatergic excitatory projections and GABAergic inhibitory projections through the commissure has been described anatomically (Hernández et al., 1996; Saint Marie, 1996; Hernández et al., 2006). All these previous studies revealed that two ICs are structurally and functionally correlated with each other. The abilities of frequency and temporal analysis during sound signal processing were changed while injecting kynurenic acid into a corresponding region of the opposite IC to block reversible excitation of CoIC to the recorded IC, thus CoIC's modulation is likely to be essential for interactions between two ICs (Malmierca et al., 2003; Malmierca et al., 2005). This kind of modulation could depend on either monosynaptic activity or multisynaptic activity (Malmierca et al., 2005).

4 The neural modulation and interaction between IC neurons

How do the neurons inside one single auditory center interact? There is little report about this interaction, but existing evidence showed there were extensive excitatory and inhibitory interactions and modulations between IC neurons in isofrequency and nonisofrequency laminas. These effects observed in previous studies were mainly inhibitory, and the percentage of excitatory role was relatively low (Jen et al., 2002a, b); GABAergic and Glycinergic inhibitions contribute to these inhibitory

effects (Xu et al., 2006; Wu and Jen, 2008). Moreover, the smaller the difference of best frequency between neurons is, the stronger the interaction is (Jen et al., 2002b).

However, the possible mechanism of interaction between neurons in one IC was revealed by electrical stimulation in ipsilateral IC. Focal electric stimulation of collicular neurons evoked the BF shifts of collicular neurons located near the stimulated ones, but the BF shifts did not occur when AC was inactivated by atropine. Therefore, it is suggested that the BF shifts elicited by focal electric stimulation of nearby collicular neurons depends on the IC–AC–IC corticofugal system (Fig. 1f–a–g), not the intrinsic collicular neural circuit (Zhang and Suga, 2005). It is shown that lower auditory central neurons are modulated mainly by the descending corticofugal system from higher level auditory centers during acoustic information processing.

5 The neural modulation to IC from other sensory centers

As far as the auditory system is concerned, neural modulation not only exists between different level auditory centers and between neurons in the same center, but also exists between the auditory center and other sensory centers. A recent study about auditory response modulated by vision in barn owl IC is a representative example demonstrating that moment-to-moment visual stimulation and excitation could enhance the auditory responses, which in the short-term increase auditory responses to salient bimodal stimuli and in the long-term could serve to instruct the adaptive auditory plasticity necessary to maintain accurate auditory orienting behavior (Bergan and Knudsen, 2009).

6 The plasticity related to neural modulation in auditory centers

The stimulus pattern usually used in studies associated with neural modulation and plasticity in the auditory center is a basic combination of acoustic stimulus and electrical stimulus which makes the signal of acoustic stimulus become behaviorally relevant to an animal. Many previous studies showed that the effect of modulation vanished within 5–10 s when a combination of acoustic and electrical stimuli was presented to the experimental animal in short time, but persisted up to 5–35 min, even 3 h long after a long-term combination of acoustic and electrical stimuli (Zhou and Jen, 2000b; Ma and Suga, 2001b). That is to say, the neural modulation could not only affect the ongoing signal processing but also elicit plastic changes in the auditory system.

A generally accepted hypothesis about plasticity is that in the critical period of neural circuit development there are active cell growth and molecular environment which is beneficial for axon growth. Thus, the weakening of the central auditory system plasticity in adult animal may be due to stabilization of molecular structure in auditory neurons. Another possible reason is that specific, protected connection patterns have not formed in neural circuits. The accuracy and connection degree of neural circuits determined by heredity is still very low during development of the central auditory system. So it is necessary for the specific spatiotemporal response pattern induced by experience to continuously strengthen and sharpen the fragile connection (Fritz et al., 2003; Wu et al., 2004a, b). However, the central auditory system of adult animal is not unalterable, either. Numerous evidences from animals and humans have indicated that AC or AI is continuously reshaped in task- and experience-dependent ways. The reorganization could be observed at the level of RF, topographic maps and brain activations measured by using neuroimaging methods (Black et al., 2006; Thiel, 2007). Such an experience-dependent reorganization is attributed to several neuromodulatory systems (Suga and Ma, 2003), such as cholinergic, noradrenergic, dopaminergic and serotonergic modulations; in particular, Ach is essential for the formation of rapid plasticity. For example, a centripetal long-term BF shift toward frequency of conditioned pure tone stimulus was observed in the AI of the big brown bat, *Eptesicus fuscus*, when a fear conditioned stimulus was presented for 30 min (Gao and Suga, 2000). It was explained as that the auditory fear conditioned stimulation activated the neural circuits of the AI and the corticofugal system to elicit a small range of short-term BF shift; in the meantime, synchronal presentation of conditioned and unconditioned stimuli could indirectly increase cortical acetylcholine release from the cholinergic projection of basal forebrain and make the BF shift large and long-term (Ji and Suga, 2007). However, little is known about the exact mechanism of the central auditory plasticity in adult animals at present. As the complicated interactions and integrations between neurons in the auditory center (Zhang and Suga, 2000), and many parallel connections and feedback loops in the auditory pathway, the plastical changes we observed in a certain area were likely dominated by higher, lower or parallel auditory structure. Therefore, it is difficult to determine the exact brain structure which induces the auditory plasticity. Two studies that focal electric stimulation of auditory and/or somatosensory cortices could evoke plastical changes of bat's central auditory system revealed two brain structures, AC and IC, involved in plasticity at least (Gao and Suga, 2000; Ma and Suga, 2001b). Another recent study also showed that there were specific and nonspecific plasticity of the primary auditory cortex elicited by activation of the ascending auditory thalamic projection to primary auditory cortex (Ma and Suga, 2009). The study of Zhang and Knudsen (1999) in owl auditory midbrain even provided a more direct evidence. They found that there were some

plastic changes, i.e. formation of some new connections, between ICx and ICc during formation of interaural time difference representation, which would persist until animal's adult stage. The connections acquired by learning were mainly mediated by N-methyl-D-aspartate (NMDA) receptors; otherwise the shaping of connection pattern was mediated by GABA receptors (Feleman et al., 1996).

In a word, studies of neural modulation and auditory plasticity have attracted much attention and become hotspots in recent years. With the rapid development in hearing research, a lot of achievements have been made in the fields of neural modulation and auditory plasticity, which also have become important basis for the studies of auditory cognition, auditory learning, and memory because of the close relationship between these research areas. Since there are still many unanswered questions for studies in neural modulation and plasticity of IC and other central auditory structures, more investigations are required.

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