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THE FUNCTION OF OFFSET NEURONS IN AUDITORY INFORMATION PROCESSING

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Abstract

Offset neurons which respond to the termination of the sound stimulation may play important roles in auditory temporal information processing, sound signal recognition, and complex distinction. Two additional possible mechanisms were reviewed: neural inhibition and the intrinsic conductance property of offset neuron membranes. The underlying offset response was postulated to be located in the superior paraolivary nucleus of mice. The biological significance of the offset neurons was discussed as well.

Keywords

• Offset neuron • Discharge pattern • Neural mechanism • Temporal information processing

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1. Introduction

The offset responses or neurons were first demonstrated in the visual system in the 1930s and were intensively studied thereafter [1-5]. In the auditory system, offset neurons were first reported in the bat cochlear nucleus (CN) and inferior colliculus (IC) [6], then in the auditory nerve (AN) [7], the CN [8], the medial geniculate body (MGB) [9] and auditory cortices (AC) [10,11] of cats, the mouse auditory brain stem [12,13], the human auditory cortex [14], the frog AN fibers [15], and the rabbit superior olivary complexes (SOC) [16]. Even though the proportion of offset neurons in the auditory system [17-20] is much lower (< 30%) than in the visual system, offset neurons are almost universally recorded with auditory evoked potential (AEP) recordings, *in vivo* extracellular recordings, *in vivo* intracellular recordings and *in vitro* voltage clamp from the peripheral AN [21] to various nuclei [16,22-24] of the auditory brain stem pathway and AC [25,26] in different animal species.

Previous studies observed that there is a significant asymmetry in the neurophysiological and perceptual processing of stimulus onsets and offsets [27-29]. The origins of the asymmetries of psychophysics and neurophysiology have a common response threshold mechanism which adaptively tracks the ongoing level of stimulation [30]. For auditory processing and complex distinction, since sound duration is considered to be one of the essential information [31], offset responses encoding the sound termination may play an important role. As is well known, onset neurons respond to a stimulus but cannot distinguish the cessation of one [32]. Auditory system requires knowledge of the termination of the tone in order to avoid illusory continuity of the tone [33]. The reason as to why there are offset responses has received little attention but perhaps this is due to difficulty in recording. Only a small number of offset neurons were observed in most studies [34-36]. Furthermore, the failure to record offset responses may be attributed to barbiturate anesthesia used in the experiments, since a large number of offset responses have been reported from awake or ketamine anesthetized animals [37-40]. Given the potential functional significance, the offset response should be further investigated. Until now we have not seen a review about offset responses, so it makes sense to review recent findings about the characters and mechanisms as well as biological meanings of offset responses.

2. What is offset response?

In general, acoustic neuronal response to stimulation can be divided into spontaneous and evoked responses. Furthermore, evoked responses may be divided into onset response, offset response, onset-offset response, and sustained response, depending on the action potential (AP) firing triggered by the beginning or the end of the acoustic stimuli [31]. Different response patterns could represent distinct physiological implications [41], and have special local neuronal circuits [42]. Due to the fact that the responses coding the termination of the sound contain offset and onset-offset responses, some onset-offset neurons could be changed into offset responses under some stimuli conditions [20], so the offset response that is reviewed also includes the onset-offset response. Moreover, based on the pattern of peri-stimulus-time histograms (PSTH), the offset neurons can be classified into four types: offset, onset-offset, onset-sustained-offset, and inhibition-offset (Fig. 1) [31].

Most neurons of the central auditory pathway develop responses that are dominated by onset responses [30]. Sometimes the onset response may be represented by a single spike or a burst of spikes [43,44], which may be shaped by both adaptive and post-inhibitory onset responses [43,45]. To some extent, the brevity of the response is beneficial to ongoing acoustic streams. It becomes clear that the onset response is not driven directly by the

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amplitude level of the sound, but by the transient onset ramp (rate of pressure change, in the case of linear rise-time pulses) of the stimulus. This precise temporal characteristic makes it a hallmark for the induction of sound, but it cannot detect the termination of the sound. Considering that the successful auditory scene analysis requires the preservation of timing information [46], the offset response could be a candidate.

3. Factors influencing the offset response

Despite the potential functional significance of offset responses, they have received relatively little attention compared with onset neurons, partially due to their small numbers (< 30%) [17-20]. More prominent offset responses obtained from A1 of animals reported recently that they were either awake [38,39,44] or were anesthetized with ketamine or halothane [37,47]. According to Zurita *et al*. [10], offset neurons under pentobarbital anesthesia were less evident than under nitrous oxide anesthesia, which could be a reason why few offset neurons were recorded using in *vivo* single-unit extracellular recording under pentobarbital anesthesia [34]. Another reason may be that offset neurons are site-specific, the onset-offset neurons are located only within the dorsoposterior division of the central nucleus of the IC (ICc) [19,48,49], and offset neuron clusters are always segregated from onset neuron clusters and form offset sheets in various divisions of the MGB [20,24]. Besides the above-mentioned causes, rise-fall time, intensity, frequency, as well as duration of the sound stimulation were found to be influencing factors.

3.1 Rise-fall time

The offset of auditory brainstem response (ABR) strikingly decrease, eventually disappearing, as the fall time was prolonged from 0.2 to 2 ms [48]. Henry [13] and Van Kampen *et al*. [50] also showed that offset responses were sensitive to both rise and fall time. There is a possibility that short fall time may make the rebound offset more synchronous, hence facilitating the offset responses [51].

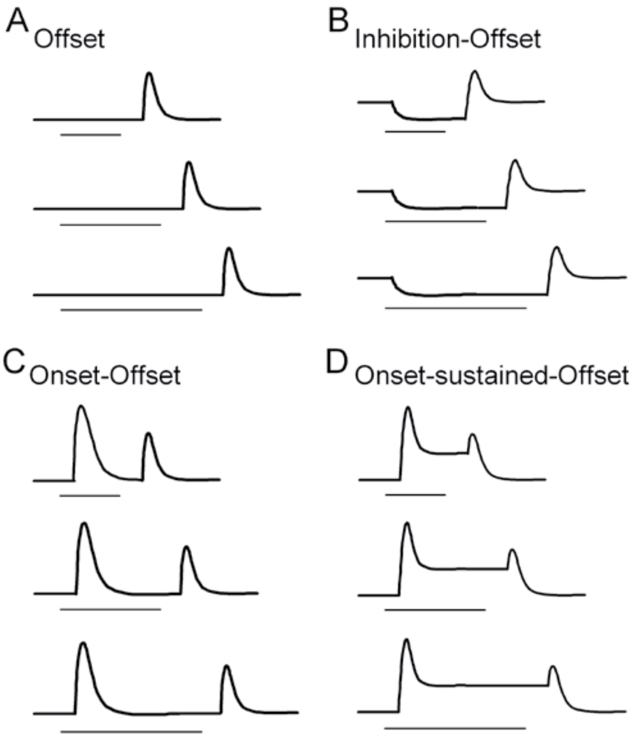

Figure 1. Schematic diagram illustrating four response patterns of offset neurons. A-D, the four response patterns of offset neurons under stimulation conditions of three durations; the bars of different length below every response indicate the tone duration.

3.2 Stimulus intensity dependence

The stimulus intensity can effectively influence the discharge patterns of auditory neurons. Studies about offset neurons generally show that they have significantly higher thresholds than the onset neurons, meaning they will not evoke offset responses if the stimulus intensities are below the thresholds of offset neurons, although the onset response may be present. This tendency is applied to bats such as *Rhinolophus megaphyllus, Rhinolophus philippinensis, Hipposideros diadema, Taphazous georgianu* [52], *Aseuiscus tricuspidatus* [48], guinea pigs [24], rats [51], mice [31], as well as humans [53], but independent of recording methods. Using AEP recording, compared with the amplitude of onset response increasing monotonically with intensity elevation, the amplitude of offset ABR goes through a maximum [48], sometimes will reduce with further increase of stimulus intensity [54], while the number of action potentials (APs) continuously increases with sound intensity increasing in the superior paraolivary nucleus (SPON) of mice using single-unit recording [40], this discrepancy may be induced by the recording methods or the difference between nuclei because the ABR amplitude depend on the synchronization of neuron population and some neurons may change their discharge patterns with intensity changing. He [20] also demonstrated that most of the onset-offset neurons in MGB of guinea pig changed to either onset or offset response as the stimulus changes.

Our lab also recorded one neuron with onset-offset response to constant frequency (CF) stimulus in the IC of *Hipposideros armiger* [35]; it is also of interest that when stimulated with constant frequency - frequency modulation (CF-FM) sounds, we observed two types of responders, single-on (SO) and double-on (DO) responders [35,55-57]. The DO neurons, generating responses to the onset of CF and

FM components, respectively, are different from the onset-offset neurons. Some SO neurons could change to DO neurons as sound intensity and duration increased. It is even more intriguing what the response pattern of the neuron that elicited onset-offset response to CF stimulus will be when stimulated with CF-FM sounds (a promising new line of research on this issue is under way in our lab).

In practice, considering the two factors we have referred to in Part 3.1 and 3.2 and the notion that onset responses were sensitive to the onset ramp [30], we think that the offset (and onset) ramp, but not the fall time and plateau level of the stimulus, is the effective parameter influencing the offset response. Further studies are needed to confirm or refute this claim.

3.3 Frequency selectivity to sound stimulus

In bats, the prominent offset responses were sensitive to the narrow frequency near the dominant CF [48,52,58-61]. In early studies of Grinnell [48,58], the best frequency (BF) of offset response in some CF-FM bats vary due to their distinct dominant frequency. Suga and colleagues [21,49,62] mentioned that offset responses are tuned between 58 and 62 kHz, and onset-offset neurons in *Pteronotus parnelli* have BF below 63 kHz [19,63]. Compared with BFs of the onset neurons, BFs of the offset neurons in *Rhinolophus megaphyllus* and *Rhinolophus philippinensis* were lower, while BFs of those offset neurons in *Hipposideros diadem* and *Taphozous georgianus* were higher [52]. Henry [13] showed that offset responses had two peaks with one at a frequency above the onset BF and another below the onset BF. Scholl *et al*. [64] also demonstrated that offset responses in rats typically tuned 1-2 octaves above onset response, which is in accordance with reports that cortical onset responses are complementary tuning with offset response in awake primates [25,39]. However, the frequency tuning of onset and offset neurons showed the diversity when tested in cats who were awake [38]. This unconformity phenomenon could attribute to species difference or distinct anesthesia used in the experiment, and we can also see that the offset responses are selectively tuned to a specific frequency range.

3.4 Sound duration

Although it was not specifically stated in previous studies, some of the duration-tuned neurons in the bat IC looked like offset neurons [65,66], and our study on Horseshoe bat IC found that long-pass neurons showed offset response [34]. What is more, some duration-tuned neurons in the midbrain of the mouse and the chinchilla are offset neurons [67,68], it was found that the offset neurons in the auditory cortex also had duration selectivity [11], while all the offset neurons in the auditory thalamus of guinea pigs are long-duration-selective [20]. A previous study showed that the sound stimulus of the high intensity, short rise-fall time and long duration could facilitate offset responses [51]. Our recently unpublished data also showed that offset responses were sensitive to long duration, high intensity, as well as specific frequency (Fig. 2).

4. The possible neural mechanism of offset response

In the visual system, these offset responses or neurons are thought to arise from push-pull synaptic interactions between opponent bright- and dark-sensitive (i.e. onset and offset) pathways that originate in retinal bipolar cells and remain anatomically segregated until they converge onto visual cortical neurons [69-71]. While in the auditory system, which does not show opponent processing, the mechanisms underlying offset responses that have been

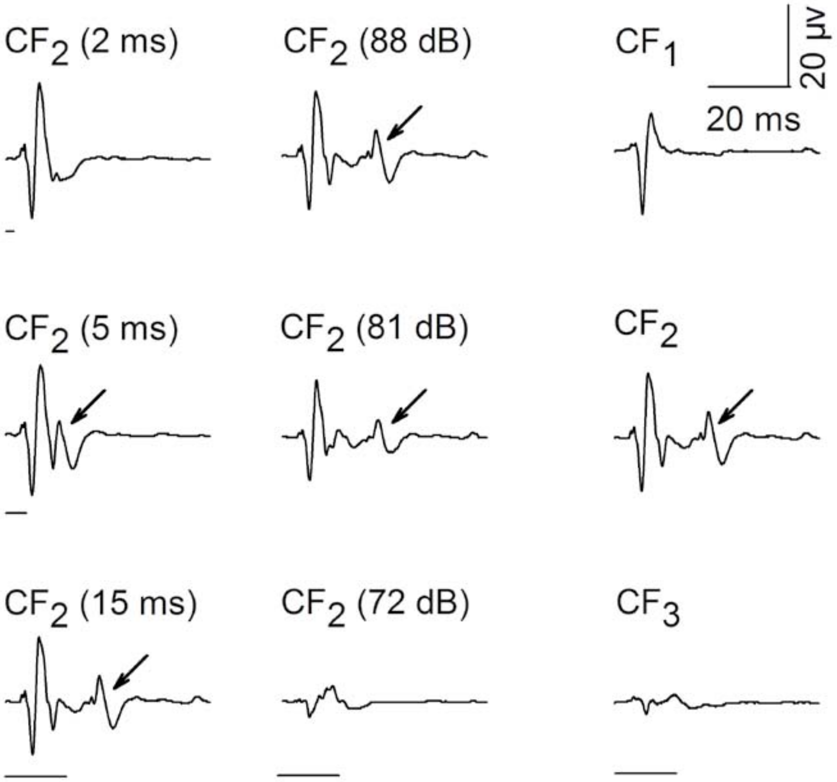

Figure 2. The effect of sound duration, intensity and frequency on the offset response of auditory evoked potential elicited by CF_1 (30 kHz), CF_2 (60 kHz) and CF_3 (90 kHz) prepared according to recorded echolocation signal emitted by Pratt's leaf-nosed bat, *Hipposideros pratti*. A, Responses to 3 sound durations (2, 5 and 15 ms) of CF_2 stimulus at 88 dB sound pressure level (SPL); B, Responses to 3 sound intensities (88, 81 and 72 dB SPL) of CF_2 stimulus with 15-ms duration; C, Responses to CF_1, CF_2 and CF_3 under stimulation condition of same intensity (88 dB SPL) and same duration (15 ms). The arrows above recorded traces indicate offset responses. Bars of different length below recorded traces represent respective sound duration. Right angle at the top right corner of recorded CF_1-trace in panel C represents time (ms) and amplitude (μV) scales of the auditory response (our recent unpublished data).

studied extensively in many auditory nuclei are controversial. At first, the offset responses found in CF-FM bats have been considered to be a rebound from neural inhibition [59], or a rebound excitation following non-neural suppression in the cochlea [48,72], or associated with a mechanical transient occurring in the inner ear [49,73,74]. Offset responses may have been widely accepted to arise from post-inhibitory rebound [30,51,75]. Until now, the two postulated mechanisms, i.e. the neural inhibition and the intrinsic conductance property of offset neuron membranes, from the studies on mice SPON are more acceptable explanations and they have been validated in SPON of mice [31,40]. SPON is one of the prominent cell groups which comprise the periolivary nuclei of the SOC that receive predominantly contralateral excitatory input from octopus and multipolar cells of cochlear nuclear complex [76,77] and a substantial, tonotopical inhibitory input from the ipsilateral medial nucleus of the trapezoid body (MNTB) [78,79].

4.1 Neural inhibition

Neural inhibition plays an important role in shaping the discharge pattern of offset neurons. When the inhibition accepted by offset neurons was discontinued, the offset response would change [80,81]. Therefore, we postulate a model which interprets this phenomenon (Fig. 3A). When an early inhibition and a late excitation evoked by a sound stimulus arrived in a convergent fashion to offset neurons, an interaction between them was generated, which induced hyperpolarization of a short duration and depressed the great mass of excitation. After the inhibition ended, the residual part of the excitation burst APs, i.e. offset response. A previous study has demonstrated that the offset firing is mediated by a glycinergic receptor. The glycinergic inhibition from MNTB to SPON may be stronger than the excitatory synaptic projection from CN, and it makes firing impossible during the duration of the sound [81]. However, more details of offset response still need further study through intracellular or patch clamp recording.

4.2 Intrinsic conductance properties of offset neuron membranes

Releasing from MNTB inhibition is unlikely to be the sole mechanism underlying the offset response due to the fact that the medial superior olive (MSO) and lateral superior olive (LSO) of SOC also receive inhibitory synaptic input from MNTB, although they rarely exhibit offset discharge [82,83]. Koop-Scheinpflug *et al.* [40] demonstrated that offset firing is an intrinsic property of SPON neurons, attributed to a large electrochemical chloride gradient combined with a hyperpolarization-activated cation current (I_H), and a low-voltage-activated Transient-type Calcium current (I_{TCa}), using sound-evoked single-unit recordings *in vivo* and voltage clamp *in vitro*. I_H, unlike most other voltage-gated ion channels activated by depolarization (such as K$^+$, Na$^+$), is activated by membrane hyperpolarization from a hyperpolarization-activated and cyclic nucleotide-gated channel (HCN) with four subunits (HCN1-4) in mammals [84-86]. The immunolabeling studies showed that HCN1 and HCN2 were largely expressed in SPON cell bodies, while HCN3 and HCN4 were nearly absent. Once activated, a mixed inward current of K$^+$ and Na$^+$ reduces input resistance

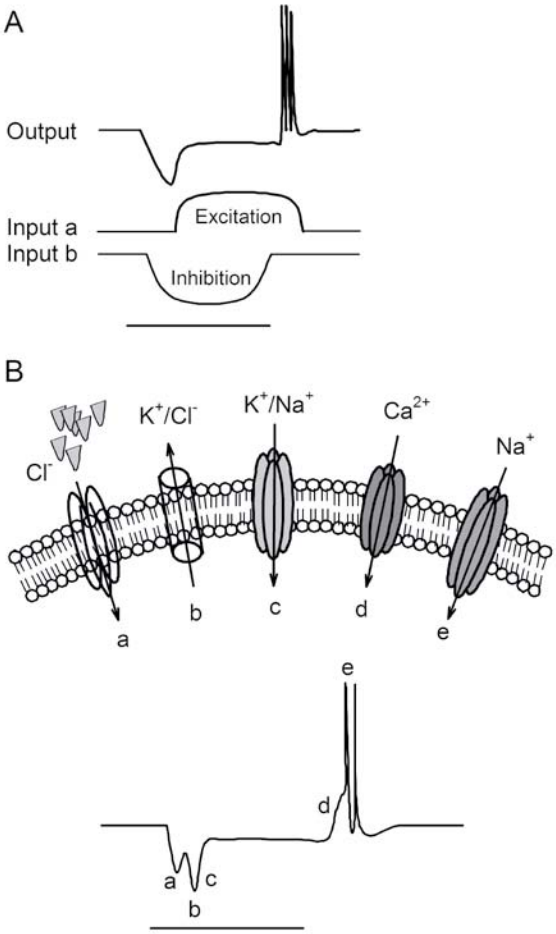

Figure 3. Schematic diagram of two possible mechanisms underlying the offset response. A, Showing the formation of offset response (upper trace, output) through the interaction between a late excitatory (a, middle trace) and an early inhibitory (b, lower trace) inputs to the offset neuron elicited by sound stimulus. The bar (bottom) represents sound stimulus. B, Upper illustration of cell membrane summarizes various ions (K$^+$, Cl$^-$, Na$^+$, Ca^{2+}), transporter (b), receptor-gated (a) and voltage-gated (c-e) channels involved in shaping offset response. Middle trace represents the changes of recorded membrane potential corresponding to a, b, c, d and e in the upper illustration. The bar (bottom) represents the sound stimulus. See text for details.

and hence accelerates the membrane time constant. Sound activates glycinergic inhibitory projections to the SPON and membrane-associated immunoreactivity of the K^+-Cl^- co-transporter (KCC2) which is found in every SPON already at times when glycine was still depolarizing [87]. By outwardly extruding chloride, KCC2 makes an extremely negative chloride reversal potential (E_{Cl}) possible, and therefore a large IPSPs in SPON. The large IPSPs activate the I_H producing the inward current and remove steady-state inactivation of Na_V and I_{TCa}. Upon termination of the sound, I_{TCa} was active over several tenths of milliseconds within a limited voltage range, during which the membrane voltage reaches the threshold of spike firing, and fast depolarization is generated to give precise offset firing (Fig. 3B).

The above two models seem to explain the SPON offset or inhibition-offset types classified in part 2, but what about the other two types? Some neurons of the CN exhibit onset-offset responses to sound stimuli, the giant cells in the deep layer of the dorsal cochlear nucleus (DCN) make excitatory projections to the contralateral IC [88]. Furthermore, the giant cells share some features with offset neurons of the IC, which may be the source for ascending synaptic inputs to elicit offset responses [68,89]. Given that cells within the ventral nucleus of the lateral lemniscus (VNLL) respond to tones with a single precise onset response [90,91], and that SPON and VNLL neurons are respectively GABAergic and glycinergic, and both provide inhibition to the ipsilateral IC [92,93], the convergent inputs from SPON and VNLL to IC may explain the onset-offset responses with IPSPs both at the onset and offset of the tone in the auditory midbrain [94-96]. These speculations might suggest that offset neurons (except onset-sustained-offset type) that arise *de novo* in some auditory nuclei maintain their original function, while some inherit ascending synaptic information [31], which also suggest that onset and offset responses may be encoded by distinct acoustic channels. This speculation is consistent with the study by He [20] for onset and offset pathway segregation in the auditory thalamus. He confirmed anatomically that onset cells are found mainly in the core of the ventral division of MGB (MGBv), whereas offset neurons form clusters at MBGv periphery and could also be found within other divisions of MGB. Scholl *et al.* [64] also demonstrated that onset and offset responses in rat AC are driven by largely non-overlapping sets of synaptic inputs, which may be attributed to the distinct projections from both MGBv and neighboring nuclei to A1 [97]. Due to the fact that similar onset and offset neurons segregate in the retina and lateral geniculate nucleus, they resemble simple and complex cells in the visual cortex [70]. In the auditory cortex, there are also simple cells with discrete onset/offset-response areas and complex neurons with mixed onset/offset-response areas [98]. However, the underlying mechanism of the onset-sustained-offset type neurons has been not well understood.

Because the sound duration in different animal species represents distinct neurobiological meanings, and there are various patterns (i.e. offset, onset-offset, onset-sustained-offset and inhibition-offset types) representing the offset response, the different explanations to the mechanisms underlying the offset response in the central auditory pathway may also be necessary [65,99,100]. However, a general role of offset responses is found in the encoding of sound termination. In this view, several offset neurons with diverse characteristics may collaborate to represent specific sound duration and sound characteristics.

4.3 Local neuronal circuits shaping the offset response

Given that the local neuronal circuits may shape the special discharge patterns [42], the four types of offset response patterns we referred to above (see part 2, and part 4.2) and may have several specific neuronal circuits. Combined with the diverse and likely mechanisms forming the offset response, the offset response pattern may be elicited by direct excitatory synaptic inputs at the end of the sound; the post-inhibitory rebound [95,101,102] (or the intrinsic conductance property) (Fig. 4A) or the interaction between late excitatory (input a in Fig. 4B) and early inhibitory (input b in Fig. 4B) inputs may induce inhibition-offset pattern; while the early excitatory input (input a in Fig. 4C), the late inhibitory input (input b in Fig. 4C) with the post-inhibitory rebound (or the intrinsic conductance property) may shape the onset-offset response pattern; and by analogy we also speculate the possible neuronal circuit for the onset-sustained-offset response pattern (Fig. 4D), i.e. the early excitatory input (input a), combined with the late excitatory (input b) and inhibitory (input c) inputs. Note that Fig. 4 represents only one of the possible neuronal circuits shaping the offset response pattern shown in Fig. 1. There may also exist other neuronal circuits shaping the offset response patterns that are currently unknown.

5. Possible biological significance of offset neurons

5.1 Duration selectivity and duration tuning

Actually, biologically important sounds including communication sounds among and within animal species, echolocation calls emitted by bats and human speech sound etc, which are typical complex sounds characterized by some parameters such as temporal, frequency, and intensity. Duration, one of the temporal features, is a simple but important one in signal recognition and feature detection. For example, in the basic sound parameters such as the frequency, amplitude or intensity and duration of vocal sound of bats, the duration is only one unchanged parameter in echo, so it is called "tag sound character" [61]. Previous extensive studies on sound duration show that most neurons in the auditory nucleus above IC responded maximally to a specific or a range of durations, which are called duration-selective neurons such as short-pass, band-pass and long-pass and their responsive range to sound frequency is called duration tuning [99,103-106]. Despite these studies [66,103] nothing was specifically stated regarding the duration-selective neurons being relevant with offset response. Some of the duration-selective neurons in the bat IC looked like offset neurons. In addition, almost all of offset neurons in the auditory thalamus of the guinea pigs are long duration-selective [20] and this phenomenon was also observed in recent studies [38,96,107]. In conclusion, the

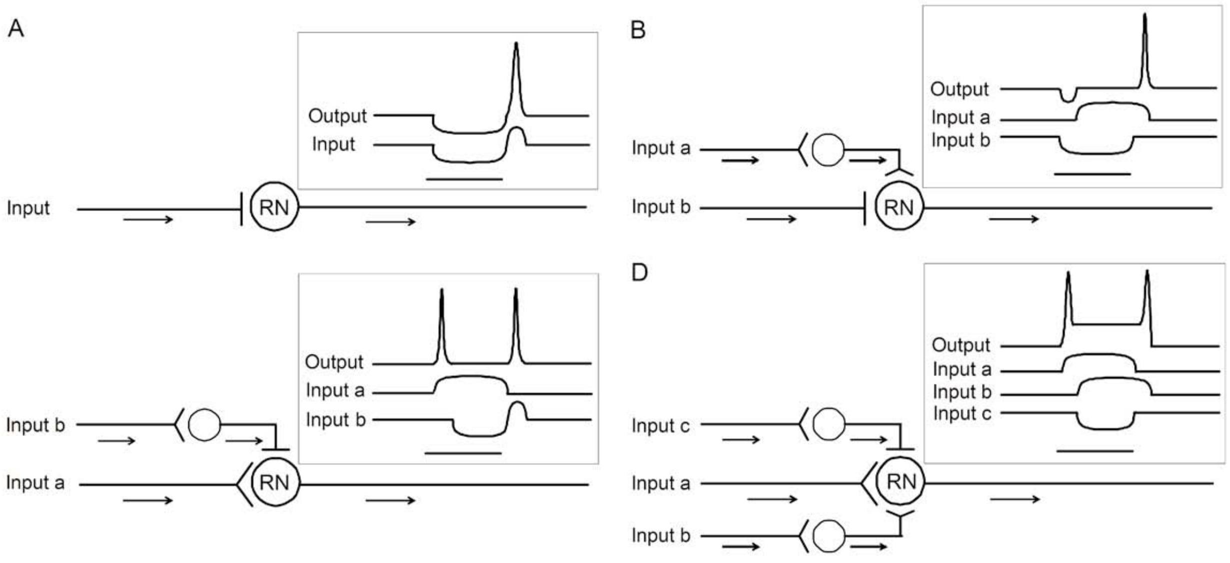

Figure 4. Schematic diagrams of local neuronal circuits shaping the offset response pattern. A, at the end of the sound, the inhibitory input depending on stimulus duration and being sustained during the sound end with an excitatory rebound, which elicits the offset response. B, the interaction between late excitatory (input a) and early inhibitory (input b) inputs to the offset neuron is shown. C, the early excitatory (input a) provide the chance for the neuron to fire to sound stimulus onset, while the late inhibitory (input b) input suppress the discharge until the sound termination, the postinhibitory rebound spiking. D, the early excitatory (input a) input, combined with the late excitatory (input b) and inhibitory (input c) inputs may explain the onset-sustained-offset response pattern. The square frame at top right corner of the local neuronal circuits shows the neuronal response pattern shaped by the interaction of multiple synaptic inputs. The bar at the bottom of the square frame indicates sound stimulus. RN: recorded neuron; ⟶: direction of excitatory conduction; ≺ : excitatory synapse; ⊣ : inhibitory synapse.

factors influencing offset firing described in part 3 and intrinsic properties of offset neurons described in part 4.2 collectively provide an insight for our understanding of the function of offset responses in duration tuning. For example, owing to the fact that activation of I_H conductance and deactivation of steady-state I_{TCa} need some time, the long duration will more easily produce the offset responses in SPON [40,64]. However, a short-duration sound with higher intensity may activate more I_H current in a shorter time and can also elicit an offset response. In this way, offset responses encode the special sound information carried by sound signal. Some onset-offset cells are also found in the auditory midbrain [93,96], which may be attributed to the convergent projections from VNLL onset encoding and SPN offset responses to IC.

5.2 Gap detection

The gap, or silent period, which is detectable between closely spaced sounds or components of sounds, is a vital sound character for sound communication of animals and human speech perception [81,108-110]. If the gap is undetectably close between sounds, it will generate the masking effect [55,111]. Offset responses are considered to play the role in gap detection, and gap detection not only depends on gap duration but also especially on pre-gap duration (i.e. sound duration before gap initiation) [112]. For instance, a 3-ms gap behind a 100-ms pre-gap is successfully detected by the neuron, while the same 3-ms gap behind 50-ms pre-gap is difficult to be detected by the neuron [40]. This is the reason that a pre-gap of shorter duration is not enough to generate a greater inhibitory temporal summation, a greater IPSP may activate hyperpolarization-dependent I_H (a complex Na^+-K^+ channel) and elicit an offset response. In addition, it is perhaps that the pre-gap of too short duration is difficult to satisfy the need of offset response latency so that offset response latency lasts to or enters into post-gap, i.e. the sound following gap, and induces the offset response depressed by IPSP evoked by post-gap [40] (also see part 4.2).

5.3 Noise rejection

Since the sound duration of animals have species-specific meanings, the offset response encoding the cessation of the sound may have special biological meanings in different animal species. As we can track back to the previous reports, the offset neurons in the auditory system were first demonstrated in the bat [6], and further studies found that those offset neurons mainly focused in long CF-FM bats which showed sharply frequency tuned with high Q-10 dB values in the neurons [48,49,58,59,62,72,73,113-116]. The prominent offset responses were sharply tuned in a narrow frequency range near the dominant frequency [48,52]. It appears to be correlated with the complex living conditions and foraging strategies of CF-FM bats. In highly cluttered narrow spaces, they must be able to discriminate the difference between echoes from targets and highly overlapping background sounds. The auditory system of these CF-FM bats in auditory structures and functions has adapted to their living surroundings: high duty cycle with a long CF component followed by a short

FM component [117], a specialized auditory fovea where frequencies around the dominant frequency, i.e. the CF of the second harmonic of the echo-locating signal, are highly over-represented [35,52,60], as well as Doppler shift compensation (DSC) that maintain the CF component of echoes within the sensitive auditory fovea [118,119]. Behavioral studies have showed that mustached bats and some horseshoe bats are adept at attacking fluttering targets [120,121], which induce the echo to generate frequency and amplitude shifts called glints [117,122], but the echo duration does not change and becomes a "tag" recognizing the echo from the target [61]. The bats can gain much information about the prey from the glints, which in turn allows them to be selective of their prey [123-126]. Because of the highly acoustical attenuation of ultrasound in the air, the amplitude of the glints is relatively stable [122], while the echoes from the background reaching to the bats' ears are ongoing amplitude modulated, most of onset-offset neurons were unresponsive to sinusoidal amplitude-modulated tone bursts (SAM), this might represent a clutter rejection mechanism for CF-FM bats focusing on dominant glints, which may make onset-offset neurons candidate for selectively responding to frequency modulation embedded in ongoing amplitude modulated background echoes [19]. Behavioral studies also demonstrated frequency shifts caused by prey fluttering are robust during capturing flight [117,122], while the bats exhibited DSC for echoes returning from stationary objects ahead of them, but not for echoes from targets [19,117,119]. Evidence that the offset response of cortical auditory evoked potential (CAEP) recorded from scalp of young adults with normal hearing were sensitive to not only signal-to-noise ratio, but also absolute signal level in background noise [127], also suggesting offset responses encoding behaviorally relevant signal level in noise may induce noise rejection.

In summary, offset responses are important cues relevant to perceptual grouping and auditory scene analysis [128]. Besides what we refer to above, it also reported that offset (or onset-offset) neurons are correlated with the motion of a sound source [129,130], the detection of interaural phase disparity [131,132], recognition of bats' communication calls [96], as well as the acoustic startle reflex [133].

6. Prospect

Although the response pattern is the basic property of auditory neurons, it may make the auditory neurons have more functions in auditory information processing. Therefore, studies on the mechanism underlying offset response and the relation between offset and onset-offset response patterns and animal behaviors would have the important significance. To further understand the synaptic mechanism of offset responses in different auditory nuclei, the experimental methods used in the future studies would be more *in vivo* intracellular recording, *in vivo* patch clamp recording and behavioral training combined with molecular-biological examinations etc. we believe that more new knowledge about this response pattern and its physiological functions in frequency tuning, amplitude tuning, forward and backward masking etc would be obtained.

Acknowledgments

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