Theme 2: Cellular mechanisms in the Cochlear Nucleus

'The Cochlear Nucleus (CN) presents a unique opportunity for quantitatively studying input-output transformations by neurons because it gives rise to a variety of different response types from relatively homogeneous input source, the auditory nerve.' (Delgutte, 2002) The tonotopically arranged auditory nerve fibers (ANFs) are first projected into the CN on their ascending afferent pathways. The tonotopical organization is maintained at the CN level, but the fibers bifurcate and synapse onto different cell types both in the dorsal and the ventral side of CN (DCN, VCN). While the peri-stimulus time histograms (PSTH) obtained at the terminal of the ANFs (pre-synaptic site at the CN) are homogeneous, PSTHs at the post-synaptic site show a number of different patterns that can be used for categorical distinctions into different neuron types. This heterogeneity of the post-synaptic response at the CN may be due to many factors, for example, it is complicated by the ANFs synapsing with different cell types, which differ in morphology, electrical properties and synaptic organization; but the exact cellular mechanisms cannot be determined conclusively due to the efferent fibers projected from higher centers also making contributions to the response. In this theme report, literature reported on the effects of the efferent descending pathways on the post-synaptic response of the CN are surveyed and a computational model of one of the CN neuron types is examined to ascertain how the electrical properties and synaptic organization might influence the post-synaptic response.

In almost all CN physiological studies, anesthetized or decerebrate preparations are used. May *et al* (1992) were able to obtain CN neuron recordings from awake and behaving animals[1]. This novel approach provided a window of opportunity to compare and contrast the recordings made on anesthetized and decerebrated with awake animals and postulate how the descending system might influence the post-synaptic response. Different neuron types found in the VCN, e.g., onset, chopper and primary-like units, were examined and the authors showed that there are no statistically significance differences amongst units obtained from the awake, decerebrated and anesthetized preparations, in terms of their average dynamic ranges of rate-level functions for tone bursts in quiet. However, all preparations showed a larger dynamic range for noise bursts in quiet which the authors attribute this increase to the effects of two-tone suppression.

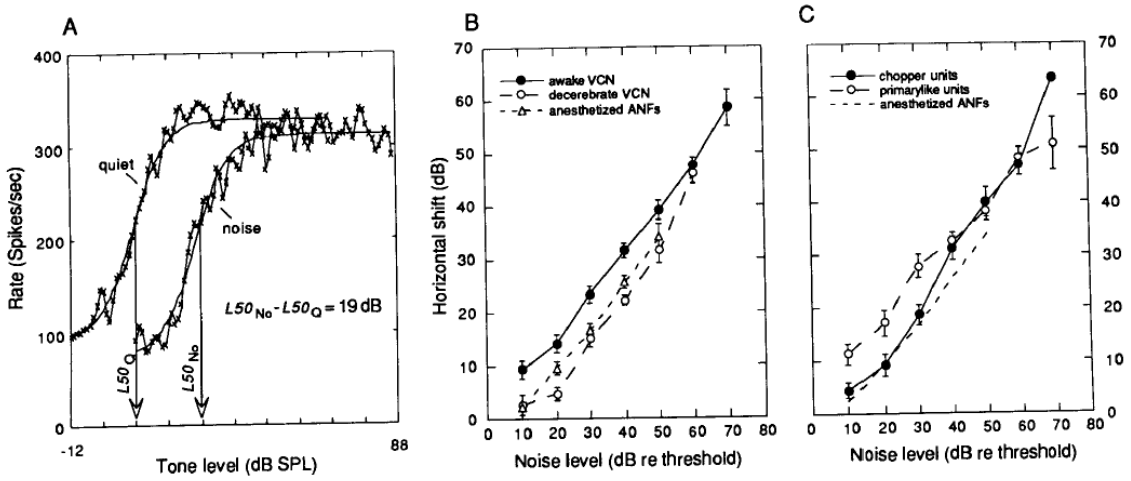

Figure 1 Noise-induced shifts of best frequency rate-level function. (May *et al*, 1992, Figure 6)

[1] Six behaviorally trained cats were chronically implanted with two devices to allow recording of neural responses in the VCN while these subjects participated in behavioral testings.

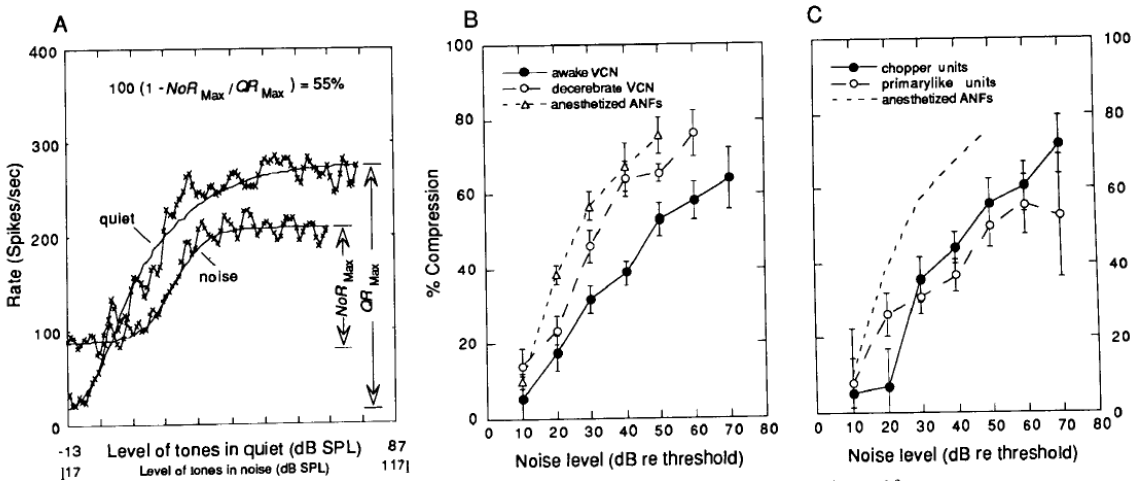

Figure 2 Noise-induced compression of best frequency rate-level functions. (May et al, 1992, Figure 7)

Figure 1A illustrates the horizontal shifts of the best frequency (BF) rate-level functions which was used by the authors to suggest the presence of two-tone suppression effect. In particular, Figure 1B shows that units in awake cats revealing an increased shift of ~6dB relative to units in anesthetized or decerebrate cats. However, there are no significant differences between the different units recorded in the VCN of the awake cats, as illustrated in Figure 1C. The noise-induced compressions[2] are also calculated and compared amongst the three types of preparations. Figure 2B shows that, consistent with the results summarized in Figure 1, units obtained from the awake cats exhibit the least compression. However, it is interesting to note that while the decerebrated VCN units show the least horizontal shift in Figure 1B, anesthetized ANF units are shown in Figure 2B to be more compressed than the decerebrate VCN units.

The above comparisons between the responses of VCN units in awake cats and those of ANFs in anesthetized cats also resemble to the increased shift and decreased compression that result from crossed olivocochlear bundle (COCB) stimulation. From Figure 3A, the authors reported that the shifts exhibited by the VCN units in awake cats were similar in magnitude to those observed for ANFs in anesthetized cats during COCB stimulation. Figure 3B illustrates that VCN units in awake cats show less noise compression than ANFs in anesthetized cats without COCB stimulation but similar compression values to those of anesthetized cats with stimulation. Assuming that the cochlea and the auditory nerves are unaffected by anesthesia, the authors argued that from the above results, the dynamic range adjustments in the VCN are strongly influenced by the olivocochlear efferents, which could very well be affected by anesthesia.

[2] Noise-induced compression C_{No} is defined by the following equation:

$C_{No} = 100.(1-N_oR_{max}/QR_{max})$ where N_oR_{max} denotes maximum driven rates in noise; and QR_{max} denotes maximum discharge rates in quiet.

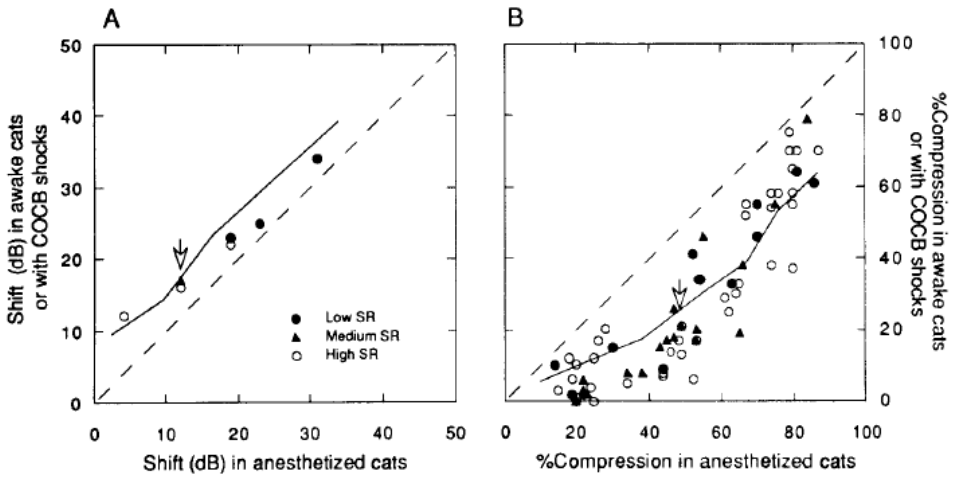

Figure 3 Scattergrams of (A) noise-induced shift and (B) compression for VCN units in awake cats and ANFs in anesthetized cats with COCB stimulation. (May *et al*, 1992, Figure 12)

May *et al* (1992) concluded from the above that the post-synaptic response is affected by the efferent system, and Kopp-Scheinpflug *et al* (2002) attempted to examine the descending system more closely by recording *[responses from CN neurons receiving]* the endbulb synapses located at the anterior part of the VCN (AVCN). Morphological data suggest that spherical bushy cells (SBCs) in the AVCN are innervated by only two to four ANFs that form large synaptic endbulbs on the somata of the neurons. In this synaptic configuration, it is possible to detect the post-synaptic action potentials (APs) of SBCs, using extracellular electrodes, which is accompanied by a proceeding 'pre-potential" (PP), indicating the pre-synaptic afferent ANF inputs. However, the authors noted that there are "isolated PPs" that are not followed by APs. The authors argued that by analyzing simultaneously the activity of the SBC and its afferent inputs (spike-proceeding PP plus isolated PP[3]), the presynaptic-to-postsynaptic input-output function can be used to consider the influence of neuronal inhibition on the activity of SBCs.

To ascertain the effects of inhibition, the authors apply strychnine and bicuculline iontophoretically to block glycinergic and GABAergic inhibitions respectively. Figure 4 shows that by blocking glycinergic inhibition, the effect of inhibition that can be seen in the non-monotonic course of the rate level function for the predrugged units in Figure 4(Top) is decreased and this spike rate takes on a monotonic cause and reverse upon recovery. The authors also showed that blocking GABAergic inhibition also increases the spiking rate.

[3] Using principal component analysis, the authors are confident that the waveforms obtained reflect the activity of the same endbulb and not due to sampling the discharges of multiple inputs.

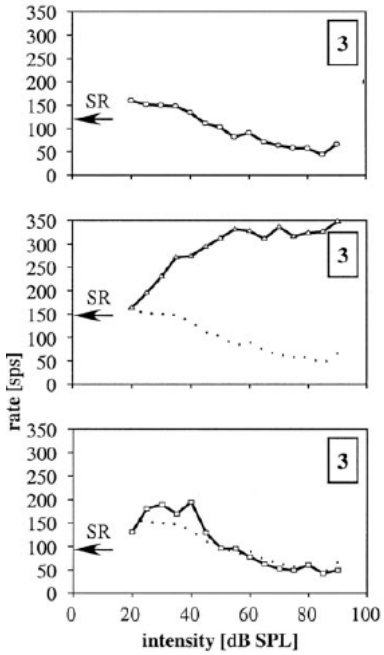

Figure 4 Pharmacological block of glycinergic inhibition in a SBC. Dotted lines indicate the predrug rate-level functions. (Top) Predrug condition; (Middle) strychnine application; (Bottom) recovery. (Kopp-Scheinpflug et al, 2002, Figure 7)

It is often difficult to separate the consequences of cochlear suppression from inhibition because both mechanisms effectively reduce the spike activity of SBCs. However, the authors argued that in their two-tone experiments, cochlear suppression would be reflected in both the presynaptic and postsynaptic activity, while an inhibiting influence can be revealed from the differences of these activities. In Figure 5A-C, the presynaptic activity shows a decrease of suppression in the high frequency sidebands, which decrease with probe levels. However, in the postsynaptic site Figure 5D-F, the high-frequency sidebands covered a wider area, which the authors argued to be a reflection of the contribution of inhibition.

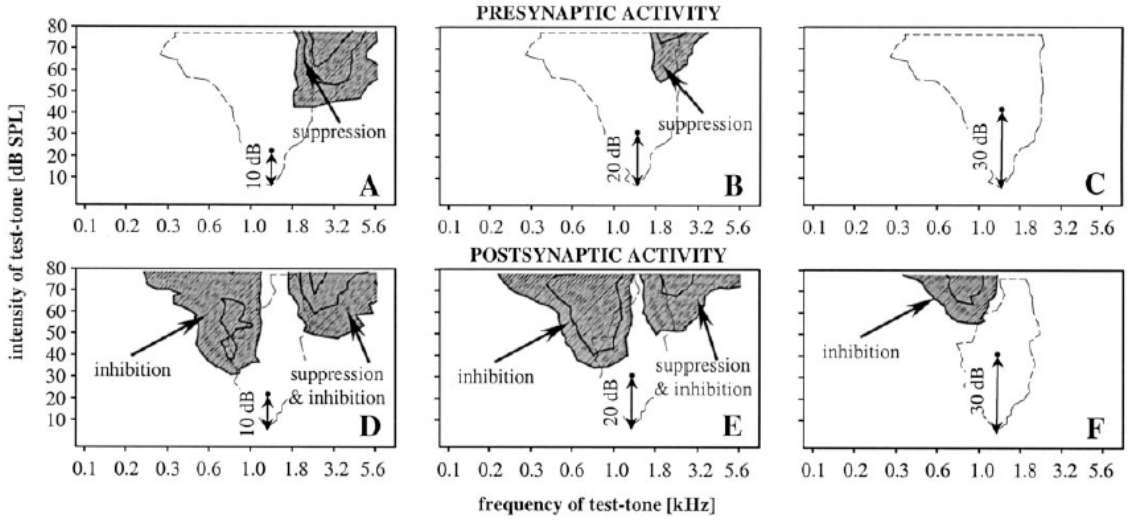

Figure 5 Distinction between two-tone suppression and neuronal inhibition. (Kopp-Scheinpglug *et al*, 2002, Figure 11)

Furthermore, the influence of postsynaptic inhibition is seen clearly in the low-frequency sidebands (Figure 5D-F), which have no presynaptic correspondence (Figure 5A-C). While the authors postulate two possible sources of glycinergic inhibition within the CN, the exact origin and the fluctuation of these inhibitory inputs still remain largely unknown.

From the above two studies, it is clear that the *descending* inputs have significant effects on the postsynaptic responses recorded at CN. Too little is known about their origin and properties to include into any computational models. Kalluri *et al*. (2003) constructed a mathematical model to simulate the discharge patterns of the CN Onset neurons assuming that the input to this model is purely excitatory. They argued that the inhibitory inputs would only influence the total input synaptic strength. Nonetheless, even with such omission in the model and a very simple R-C membrane model, insights can be gained on how the electrical properties and synaptic organization can influence the postsynaptic responses.

The authors argued that Onset neurons are particularly interesting to model since it is this type of neurons which cause the most transformation between their input and output characteristics. The aim of this paper is to use a leaky-integrator model (Figure 6) and simulate 3 types of onset neuron PSTHs: Ideal Onset (On-I), Onset with late activity (On-L) and Onset with chopping (On-C) as well as Onset neurons entraining to low frequency tones of up to 1kHz in frequency. Three main parameters are examined in this model: the membrane time-constant (τ_m), the total number of (excitatory) independent ANF input (N) and the net strength of synapses ($N.G_\alpha$). It employs a point-neuron model, whereby all synaptic inputs converge onto a single compartment and each synapse is modeled by a positive number – its synaptic weight (Koch *et al*, 2000). Due to a small number of free parameters, the implication of parametric changes can be systematically examined.

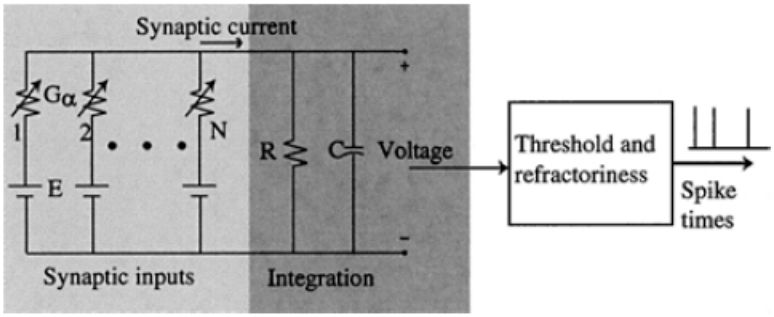

Figure 6 An integrate-to-threshold point-neuron model. (Kalluri et al, 2003, Figure 2)

The first parameter that the authors examined is the membrane time-constant (τ_m). Results show that τ_m has to be small for the point-neuron model to have the appropriate spontaneous rate to produce Onset PSTHs. It was concluded that τ_m=0.125ms, which is in correspondent to octopus cells recording *in vitro* (Delgutte, 2003). However, since τ_m being small means that the integrator is more leaky, this also implies that the model requires a large number of inputs (N) or high synaptic strength in order for the integrator to reach the threshold and cause a spike.

Figure 7 shows that from the computational model, it suggests that by increasing N, the output can evolve from sustained PSTH type to On-L and On-I PSTHs. Furthermore, if $N.G_\alpha$ is increased, On-C PSTHs can also be obtained. This finding in the computational model is compared conceptually with an analytical coincidence model, which reveals that as N increases, the normalized variance of the membrane voltage is decreased and that a threshold can be chosen such that the analytical model produces spikes at the onset but not the steady-state part of the tone burst. The increase of N in this coincidence detector model thus resembles a threshold-like input-output characteristic as shown in Figure 8. Therefore, a large number of inputs (N=400) is expected to provide Onset characteristic responses.

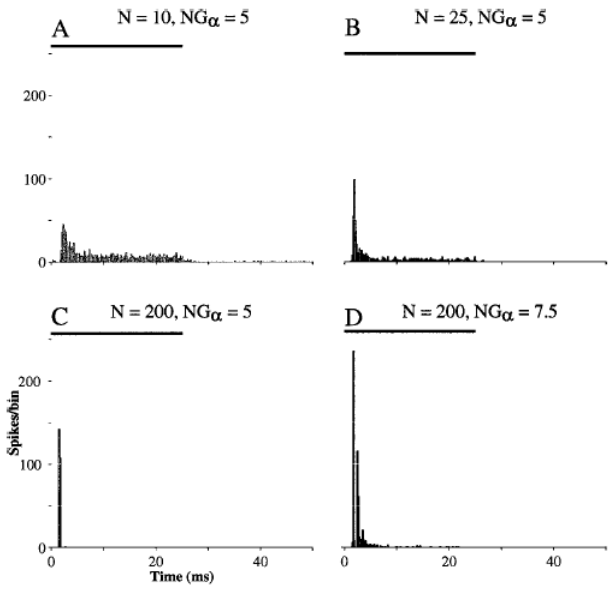

Figure 7 PSTHs for 6kHz tone bursts as a function of N and G_α in the leaky-integrator model. (Kalluri *et al*, 2003, Figure 6)

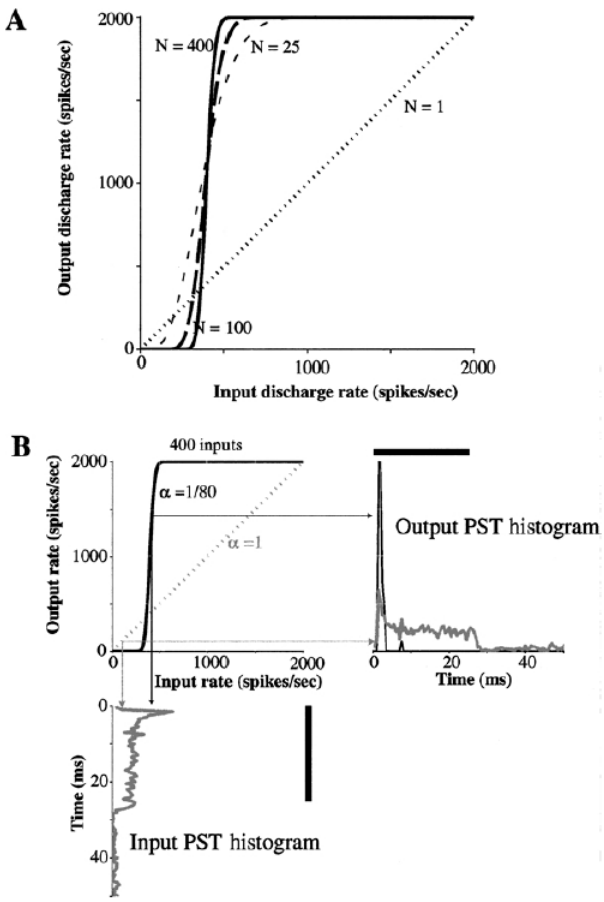

Figure 8 The transformation of input to output in the analytical coincidence detector model. (Kalluri *et al*, 2003, Figure 10)

Entrainment[4] to tone frequencies greater than 700-800Hz is remarkable since the resulting interspike intervals are close to the lower limit set by the absolute refractory period of the stimulus. As illustrated in Figure 9, $N.G_\alpha$ is an important parameter in terms of defining the bandwidth for which the model will entrain low frequency stimulus. If the synaptic strength is too high ($N.G_\alpha$=8.8), hyper-entrainment can be expected, while if it is too low ($N.G_\alpha$=5), the model fails to entrain at all. Figure 9 also shows that there is a tradeoff between the ability of the model to entrain over a broad range of frequencies and its ability to produce Onset PSTHs without chopping. Therefore, while this model can produce all 3 types of Onset PSTHs, it can only produce On-C PSTHs, and entrain low frequency tones simultaneously. From the findings in their computational modeling and analytical coincidence detector models, the authors argued that there must be a large number of weak synapses with a short membrane time constants. These properties are consistent with anatomical observations from octopus and D-stellate cells, which are putative Onset responding neurons.

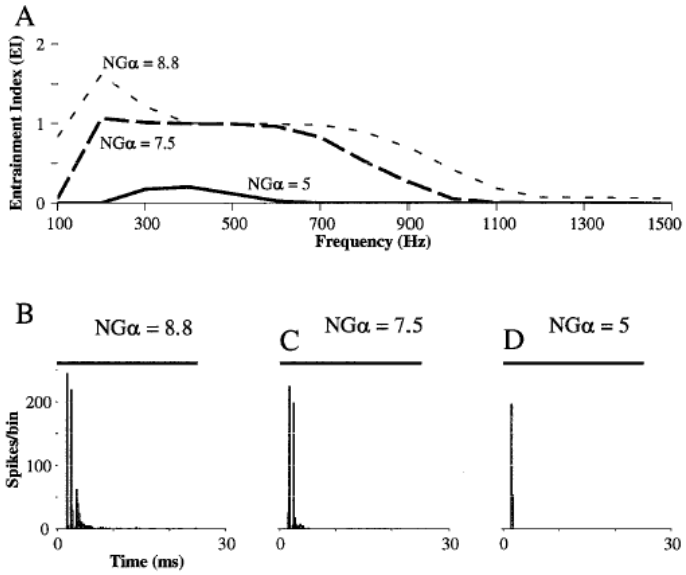

Figure 9 Entrainment to low-frequency tones and PSTHs for 6kHz tone bursts as a function of $N.G_\alpha$ in the leaky integrator model. (Kalluri et al, 2003, Figure 13)

Take home message from Theme 2

- Efferent descending auditory system can very well be affected by anesthesia. Therefore the interpretations of any neural responses must take into account on how the animal is prepared for recordings.
- Understanding the extracellular recording techniques and how to separate pre-synaptic and post-synaptic components. It is possible to postulate whether recordings have been contaminated by recording other types of cells.
- PSTHs do not conclusively characterize the response of a neuron. In the case of Onset neurons modeling, entrainment to low frequency tones is also an important consideration.
- Heterogeneity of CN neurons arising from the homogeneous AN inputs can be due to the electrical properties, synaptic organization and the possible efferent inhibition coming down from higher centers.

[4] Entrainment is the ability to discharge once on every cycle of a periodic stimulus.

Papers discussed:

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