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Involvement of GABAA-ergic inhibition and NMDA-ergic excitation in fine-grained temporal processing in audition

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The perceptual quality of successive acoustic signals drastically alters at ~30 ms of inter-stimulus intervals (ISI). For example, when click signals are repeated at ISI > ~30 ms, individual signals are clearly heard as discrete events; however, at ISI < ~30 ms, they are perceptually fused together. This ISI boundary, or "order threshold," has long been considered as an important indicator of the temporal resolving capacity of the auditory system. Several lines of evidence indicate that such distinctive perceptual qualities are mediated through qualitatively different temporal response features of the primary auditory cortex (AI) neurons: at ISIs longer than the order threshold (leading to "elemental" quality), AI neurons generate discharges time-locked to individual signals (i.e., stimulus-locking response); at shorter ISIs (leading to "fused" quality), robust discharges occur only at onset of the train of signals.

Such temporal response patterns of the AI neuron can be well captured by our neuro-computational model (Sakai et al., 2009) which incorporates temporal interplay among post-synaptic potentials (PSPs) arising in the following order with partial overlapping: (1) AMPA-receptor-mediated EPSP (latency-to-peak: 7.5 ms), (2) $GABA_A$-receptor-mediated IPSP (24 ms), (3) NMDA-receptor-mediated EPSP (50 ms) then (4) $GABA_B$-receptor-mediated IPSP (160 ms). Under this scheme, the time point of dominance transition from $GABA_A$-receptor-mediated IPSP to NMDA-receptor-mediated EPSP (~30 ms; hereafter, $GABA_A$-NMDA transition point) can be considered as the neural correlate to the order threshold (Sakai, 2011).

The above hypothesis was tested with a two-part study on adult rats and cats. First we examined how the stimulus-locking capacity of the AI neuron is affected by pharmacological treatment so as to produce a later shift in the GABAA-NMDA transition point (see above); this is archived by either up-regulating GABAA-receptors (using valproate [VPA], i.p.) or down-regulating NMDA-receptors (using MK-801, i.p.). Control animals were administered with either saline alone, or carbamazepine [CBZ], a commonly used anti-epileptic drug that does not alter $GABA_A$- or NMDA-receptor activities at therapeutic serum concentrations. We isolated single-unit activities in un-anesthetized animals by delivering a single click, then assessed its stimulus-locking capacity to click trains of variable ISI. It is noteworthy that, as compared to saline/CBZ controls, both groups administered with VPA- and MK-801 showed (1) smaller encounter probability of the unit which had stimulus-locking capacity, (2) longer cut-off ISI for stimulus-locking responses and (3) broader between-trial variance in the cut-off ISI. Onset latency to the single click did not differ among the groups. Thus, it was suggested that VPA and MK-801 decrease the robustness and reliability of AI stimulus-locking responses.

Second we examined the effect of the drugs on temporal perception. We employed a two-sound discriminative operant conditioning to train animals to respond differently to the 100-ms ISI and 2-ms ISI endpoints of click trains: for half of the animals, 100-ms ISI was assigned as "Go" signal and 2-ms ISI as "No-go" signal; for the remaining half, the opposite was the case. On subsequent generalization trials, the animals were presented with click trains of intervening ISIs. We calculated the probability for the same response (i.e., Go or No-go) as to the 100-ms ISI endpoint at each ISI, fitted data points with a sigmoid curve, and then obtained "psychometric discrimination function". Both groups administered with VPA and MK-801 showed much shallower psychometric discrimination function than the saline/CBZ controls. No difference was evident when the animals were tasked with tone frequency discrimination (12 kHz vs. 5 kHz). Collectively, it was suggested that VPA and MK-801 impaired the temporal perception necessary to distinguish elemental vs. fused quality without altering motivation, attention, motor ability or the association process.

The present findings support the hypothesis that both GABAA-ergic inhibition and NMDA-ergic excitation are critical to the temporal processing of the auditory system. One important ramification is a concern that some chemical compound with a potency to enhance GABAA-ergic inhibition and/or reduce NMDA-ergic excitation would cause a deficit in temporal processing without clear symptoms with respect to pure-tone audiometry. A growing body of evidence suggest that fine-grained temporal auditory processing, as indexed by order threshold, constitutes a bottleneck in development of verbal acuity (Tallal et al., 1993). Such a potential risk should be taken into account when initiating drug therapy, especially in young children.