## Origin of Synaptic Noise

Abstract. *The poison from puffer fish, tetrodotoxin, was applied to the kitten spinal cord. This application greatly reduced the synaptic noise recorded from lumbar motoneurons. The noise is largely evoked by nerve impulses.*

When microelectrodes were first inserted into cells of the mammalian central nervous system, in the absence of nerve stimulation it was possible to record potentials which appeared to have the same time course as excitatory and inhibitory postsynaptic potentials (EPSP and IPSP) evoked by appropriate nerve stimulation. It is generally agreed that these potentials, termed "synaptic noise," are produced by the interaction of transmitter substances with the postsynaptic cell membrane (*1*). What evoked this release of transmitter? Such a release could be evoked by nerve impulses of afferent or internuncial origin, or it could be spontaneous, analogous to the spontaneous release found at neuromuscular junctions, that is, miniature end-plate potentials. It is not known what proportion of the observed synaptic noise in the mammalian central nervous system arises from either source. Katz and Miledi claimed that most of the synaptic noise in the frog spinal cord was due to the spontaneous release of transmitter (*2*). Their results have induced investigators of the mammalian spinal cord to attribute most of the synaptic noise recorded there to spontaneous transmitter release (*3*).

However, the experiments on the frog spinal cord were not completely convincing, for two reasons. (i) Though Katz and Miledi relied on high concentrations of Mg to block nervous activity, they reported that subthreshold responses were still present in motoneurons upon strong stimulation of dorsal root or lateral column. In the frog the lateral column pathway may be monosynaptic, but the pathway from dorsal root to motoneuron is polysynaptic unless facilitated (*4*). Therefore, the variability of the latencies of these evoked responses (*2*) weakens confidence in the claim that other synaptic potentials were not evoked by nerve impulses. (ii) Katz and Miledi blocked nerve impulses completely by soaking the cord in a solution with a raised potassium concentration. Synaptic noise then increased. As the increased potassium concentration would be expected to depolarize nerve terminals and thus would greatly increase spontaneous release (*5*), we do not consider this finding evidence that all synaptic noise is of similar origin.

The possible origin of synaptic noise could be decided if one could block nerve impulse activity without otherwise interfering with the nervous system. It occurred to us that application of the poison from puffer fish, tetrodotoxin (TD), to the spinal cord might achieve this purpose, for TD is known to block nerve impulses at many sites without interfering with the spontaneous release of transmitters or the postsynaptic effects of transmitters (*6*).

In these experiments we used kittens (3 to 6 months old) anesthetized with pentobarbital sodium. Leg nerves were isolated in the left hind limb, and lumbar laminectomy was performed, the cord being sectioned at $L_2$. Kittens were chosen as the experimental animal because the recorded synaptic potentials are larger than those of adult cats and because, at the age chosen, the dissection and anesthesia present no abnormal problem (*7*). Also substances probably diffuse into the kitten cord much faster than in that of the adult cat. Synaptic noise was intracellularly recorded from lumbosacral motoneurons identified by antidromic stimulation of the appropriate ventral root and orthodromic stimulation of a leg nerve. With our usual laboratory methods (*7*), we used glass microelectrodes filled with 3*M* KCl.

Figure 1A shows the noise found in a gastrocnemius motoneuron and is typical of extensor motoneurons in kitten preparations. In this experiment, 1 ml of TD (3 $\mu$g/ml), dissolved in Krebs-Ringer solution, was then squirted from a syringe onto the area around the electrode. The synaptic noise had greatly diminished 108 seconds later (Fig. 1B). After 216 seconds, only occasional small potentials could be seen (Fig. 1C).

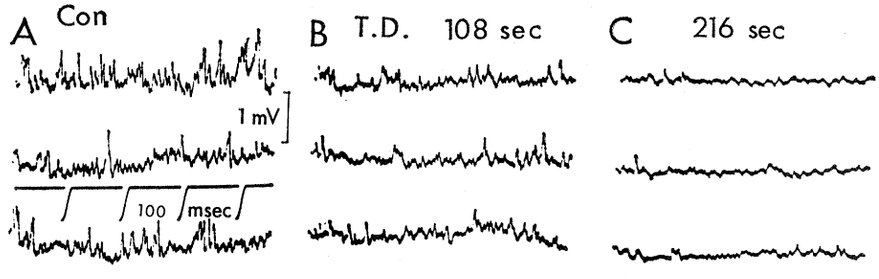


Fig. 1. Effect of tetrodotoxin on synaptic noise in a gastrocnemius motoneuron. (A) Intracellularly recorded noise; (B) 108 seconds after application of tetrodotoxin to the spinal cord area around the electrode; (C) 216 seconds after application of tetrodotoxin The records show successive sweeps of the cathode ray oscillograph at 4-second intervals.

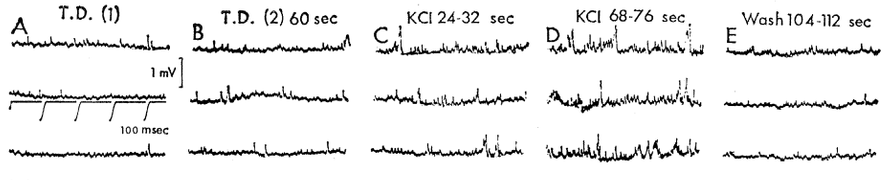


Fig. 2. Effect of K in the presence of tetrodotoxin in a gastrocnemius motoneuron. (A) Intracellularly recorded noise 10 minutes after application of tetrodotoxin; (B) 60 seconds after a second application; (C) and (D) 24 to 32 seconds and 68 to 76 seconds, respectively, after application of 0.2*M* KCl to the cord in the area around the electrode; (E) 104 to 112 seconds after KCl action was terminated by sucking off any remaining KCl and bathing the area of cord with Krebs-Ringer solution.

It appeared that most of the noise was in fact synaptic potentials evoked by nerve impulses. The alternative possibility—that TD had reduced postsynaptic sensitivity—is excluded by two findings. (i) The remaining activity is of the same amplitude and time course as that removed by TD (Fig. 1, A and C). (ii) On one occasion when only one small area of pia had been removed, TD greatly reduced the synaptic noise while hardly affecting the amplitude of the monosynaptic EPSP evoked by stimulation of the gastrocnemius nerve. Only after the noise had been reduced to the amount shown in Fig. 1C did the amplitude of the EPSP fall. Presumably in this case the myelin sheath of the afferent nerve, over most of its intraspinal course, partially protected it from the TD. Usually all in-

coming afferent volleys were blocked irreversibly after administration of TD.

In two motoneurons after administration of TD had abolished almost all synaptic noise (Fig. 2, A and B), 1 ml of 0.2*M* KCl was dropped onto the same area from which the TD had diffused. On both occasions (Fig. 2, C and D), there was a great increase in the noise; the noise returned to the control level upon washing the area with Krebs-Ringer solution (Fig. 2E). Presumably this apparent increase in the frequency of synaptic potentials was due to depolarization of nerve terminals with spontaneous release of quanta of transmitter.

We conclude that most synaptic noise is due to transmitter release evoked by nerve impulses and can be removed by abolition of nerve impulses. Burke and Nelson indeed have demonstrated that some of the noise is due to spindle afferent activity (*8*). Study of cells in the feline cortex, particularly in isolated cortical slabs, has led to the conclusion that the synaptic noise in cortical cells is mostly evoked by nerve impulses (*9*).

There are undoubtedly some spontaneous potentials analogous to the miniature end-plate potentials of peripheral synapses. Presumably the potentials which persist at a low frequency after TD (Fig. 1C and Fig. 2, A and B) are representative of these. Application of TD to nervous tissue provides an unequivocal method of clearly distinguishing such spontaneous activity from the activity evoked by nerve impulses.

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## Infant Vocalizations and Their Relationship to Mature Intelligence

Abstract. *Correlations between infant development tests and later intelligence have been found previously to be very low. Through cluster analysis, six clusters of items were extracted from Bayley's California First Year Mental Scale. One item cluster composed principally of vocalizations did significantly correlate with girls' later intelligence, increasingly so with age, and more highly with verbal than performance scores.*

It is generally believed that infant (0 to 2 years) developmental tests cannot predict the level of intelligence of the growing child or the mature adult. Virtually all developmental research reports (*1*) have reported insignificant correlations between the infant developmental test scores, which are based on extensive and somewhat similar samples of the infants' relatively limited behavioral repertoire, and later indices of intelligence. The presumption has grown that, until the effects of experience or the maturation of specific cognitive processes (hypothesis building, attention, extended memory) during the preschool years have occurred (*2*), testing infant intelligence for the purpose of estimating childhood or adult intelligence (as opposed to testing to detect infant developmental deviations) is a futile enterprise.

In arriving at this conclusion, total scores (that is, the total number of items passed) at a particular age level have customarily been used. Whether a partial score, based on an empirically derived factor or subset of items selected from these infant tests, might predict later intelligence or some factor of intelligence remained an open question. In pursuing this line of investigation, we extracted six relatively independent item clusters from the data on the 115-item California First Year Mental Scale for the total sample of children (males = 35, females = 39) in the Berkeley Growth Study (*3*). The frequent testing of these children (generally at 1-month intervals) permitted use of the age at which each child *first* passed each test item as the basic data for this analysis. This treatment of the longitudinal data permitted any test item to correlate highly with any other item, regardless of the difference in the "average passing age" of the two items, so long as the children who were precocious in passing the earlier item were similarly ranked in precocity in passing the second item. This statistical advantage, not available in factoring simple pass-fail item data from tests administered at a single age (where only a few test items are discriminating), permitted clusters to be composed of items drawn from the entire age range (0 to 1½ years) covered by the Bayley Scale.

One of the six factors which were extracted from the combined sample did appear to be related to girls' intelligence (but not boys'), as measured at years 6 through 26. Six of the seven items defining this factor involved the girls' early vocalization behavior. The items ranged in age placement on the Bayley Scale from 5.6 to 13.5 months, clearly well before the age when school-age intelligence is first predictable from total test scores. Predictability of school-age intelligence increases markedly between 2 and 4 years. A useful prediction of adult intelligence cannot be made until after 4 years of age, when verbal and performance skills have matured to a considerable degree (*4*).

The seven items and their age placements, in months, are: vocalizes eagerness (5.6), vocalizes displeasure (5.9), vocal interjections (8.1), says "da-da" or equivalent (8.5), pulls string adaptively (9.5), says two words (12.9), and uses expressive jargon (13.5). The seven items, with an average product-moment intercorrelation of .44, form a highly reliable scale (.84) as calculated by the Tryon cluster analysis computer program (*5*).

Figure 1 plots the correlations between this factor and girls' I.Q.'s from 6 through 26 years. As the girls mature, the correlations between their intelligence scores and this early vocalization factor increase, reaching a range generally between .40 and .60 during the 13- to 26-years period. For the 6- through 26-years period, the correlations for the boys' early vocalization factor with intelligence are predomi-