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# Membrane Noise produced by Acetylcholine

ELECTROPHYSIOLOGICAL studies of the motor end-plate have shown that there is intermittent release of multimolecular ("quantal") packets of acetylcholine (ACh) from the nerve terminals, resulting in the appearance of discrete miniature end-plate potentials (m.e.p.p.). The number of molecular reactions which summate to make up a single m.e.p.p. is not known; it must be very large, for—with minimal doses of applied ACh—the membrane response seems to be continuously graded, even at amplitudes which are one or two orders of magnitude below that of the m.e.p.p. (see, for example, ref. 1, page 10).

It seemed possible, however, that during steady application of ACh to a motor end-plate the statistical effects of molecular bombardment might be discernible as an increase in membrane noise, superimposed on the maintained average depolarization. Suppose, for instance, that a maintained ACh potential $V$ is made up of a statistical fusion of many "elementary" effects, each of instantaneous amplitude $a$ and exponential decay with membrane time constant $\tau$. Whether the elementary event arises from the reaction of one or more ACh molecules, with one or several receptor molecules, is left open. The average rate of such elementary effects necessary to maintain the depolarization $V$ is then given by $n = V/a\tau$. For example, if $a = 0{\cdot}1$ μV and $\tau = 10$ ms, then to produce a 10 mV depolarization requires an average frequency of $10^7$ elementary events per second. Applying Rice's theory of random noise[2] to this case, it can be shown that the expected ACh-induced voltage fluctuations across the membrane would have a root mean square value $E$ of approximately $\sqrt{Va/2}$, which, for the example quoted, is about 22 μV. Conversely, knowing $V$ and $E$, the elementary voltage amplitude $a$ can be derived.

Fig. 1 shows that ACh-induced membrane noise can, in fact, be detected. We have used either bath application of ACh or, more conveniently, local application to a single end-plate by allowing ACh to diffuse from a micropipette (placed at sufficient distance to render ineffective any possible fluctuations in position or resistance of the pipette). Membrane potential changes during ACh application were recorded simultaneously on a low gain d.c. and a high gain a.c. coupled channel (time constant approx. 0·1 s). In the experiment illustrated in Fig. 1, a maintained depolarization of 8·5 mV was accompanied by membrane noise of 29·2 μV (root mean square value). The calculated value of $a$ is 0·2 μV. Making an approximate allowance for non-linear summation of ACh potentials[3], the corrected values of $V$, $E$ and $a$ are 9·7 mV, 37·8 μV and 0·29 μV respectively. The average m.e.p.p. in this fibre (in presence of neostigmine) was 0·7 mV. Several experiments of this kind have been performed showing that the average amplitude of the m.e.p.p. is a few thousand times greater than the "elementary" ACh effect. It should be noted that the membrane noise described here accompanies ACh-induced depolarizations, but that no comparable effect was found during an electrotonic potential change of similar size, produced by passing direct current across the fibre membrane. We suggest that the membrane noise observed in these experiments arises from statistical variation of high-frequency collisions between ACh molecules and end-plate receptors.

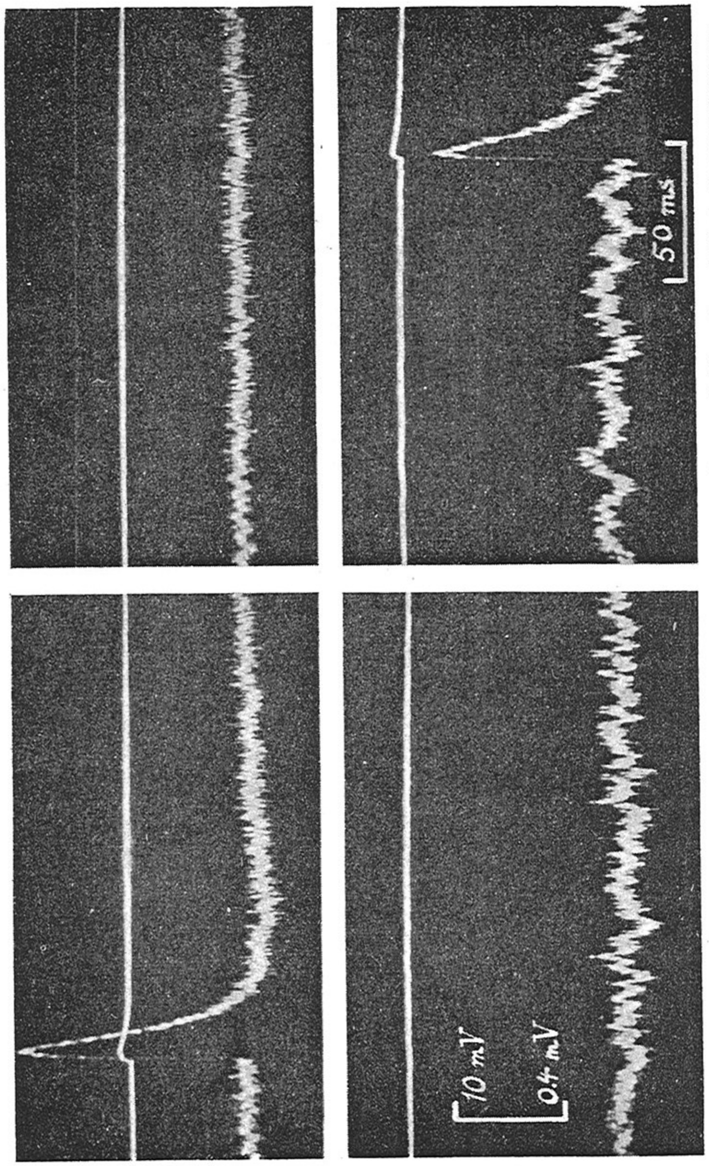


Fig. 1. Intracellular recording of membrane potential from end-plate region of frog muscle fibre. In each block, the upper trace was recorded on a low gain d.c. channel (10 mV scale); the lower was simultaneously recorded on a high gain a.c. coupled channel (0·4 mV scale). The records in the upper row are controls (no ACh); the lower row shows membrane noise during ACh application, by diffusion from a micropipette. In the lower records, the increased distance between a.c. and d.c. traces shows upward displacement of the d.c. trace because of ACh-induced depolarization. Two spontaneous m.e.p.p.s are also seen.

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