Symaptic potentials

1942, Kufflen and Katz

- Concluded that a depolarization of the end plati fired the muscle AP.

South American arrow poison CURARE

- Curare binds competitively to the nicotinic ACh receptor without opening the channel.
- Curare does not affect presynaptic or muscle AP!
- Curare reduces the amplitude of the postsynaptic potential.
- Reversal potential of the synaptic potential.

- Inject current to change the resting potential of the muscle fiber.

- What does this result tell us about the post-synaptic receptors?

- If we assume that ACh receptor is permeable to both Na⁺ and K⁺ then

\[ I_K = g_K (V_m - V_K) \]

\[ \| I_{Na} - g_{Na} V_m \| 
\]
- when we do not detect a post-synaptic potential the total current through the ACh channels must be zero
\[
I_k + I_{Na} = 0
\]
\[-g_k (V_m - V_k) = g_{Na} (V_m - V_{Na})\]
on
\[V_m = \left(\frac{g_k}{g_k + g_{Na}}\right)V_k + \left(\frac{g_{Na}}{g_k + g_{Na}}\right)V_{Na}\]
given that 
\[V_k \approx -90 \text{ mV}\]
\[V_{Na} \approx +60 \text{ mV}\]
if we assume that 
\[g_k = g_{Na}\]
then
\[V_m = \frac{1}{2} (+60 - 90) = -15 \text{ mV}\]
which is very close to the measured -20 mV

**Conclusion:** ACh receptor is an ion channel that is equally permeable to both Na$^+$ and K$^+$!

- What would be the effect of opening a Cl$^-$ selective ion channel?
- The frog endplate becomes permeable to both Na⁺ and K⁺ upon release of ACh by the presynaptic terminal — this is due to the opening of the ACh receptor channel, first observed by Neher and Sakmann in 1976. For this experiment they received the Nobel prize in 1991.

- The nature of the release mechanism

- Fatt and Katz reported in 1952 miniature (less than 1 mV) spontaneous depolarizations recorded from the vicinity of the postsynaptic membrane.

\[
\text{no stimulation} \quad V_m \quad \text{---} \quad 1 \text{mV}
\]

- Spontaneous miniature endplate potentials (m.e.p.p's)

- The shape and time course of the spontaneous mepps are similar to the endplate potential recorded during a stimulus.

- Then B. Katz did the experiment that led to his Nobel prize and the discovery of the fundamental mechanisms of synaptic transmission.
Evoked end-plate potentials were recorded in low Ca\textsuperscript{++} and high Mg\textsuperscript{++} solutions, reducing the amount of presynaptic release! The amplitude of the recorded end-plate potentials was found to be multiples of the spontaneous mepps!

- The statistical analysis of his data and found that the distribution of amplitudes was well described by a Poisson distribution whose unitary event is identical to the mepps!

Fundamentals of statistical analysis

\[N\] coins
\[p = \text{probability of heads}\]
\[t = \text{probability of tails}\]
if we toss $N$ coins the probability of a given outcome is:

$$P[\text{of one outcome}] = h \cdot h \cdot h \ldots t \cdot t \cdot t \cdot t = h^m t^{m'}$$

$$m + m' = N \text{ and } h + t = 1$$

but for $N$ coins the outcome $h^m t^{m'}$ can be obtained in many different ways,

so if $C_N(m) = \text{number of configurations when } m \text{ heads can be obtained}$

then

$$P(m) = C_N(m) \cdot h^m t^{m'}$$

but $C_N(m)$ can be demonstrated to be equal to

$$C_N(m) = \frac{N!}{m! \cdot (N-m)!}$$

then

$$P(m) = \frac{N!}{m! \cdot (N-m)!} \cdot h^m t^{m'}$$

Binomial distribution.
- The Poisson distribution is a special case of a binomial distribution.
  
  \[ P(m) = \frac{N!}{m! (N-m)!} h^m (1-h)^{N-m} \]
  
  if \( h \ll 1 \) \( \ldots \) probability of an event is small!
  
  if \( m \ll N \) \( \ldots \) number observed is small!
  
  then \( (1-h)^{N-m} \approx e^{-Nh} \)
  
  and \( \frac{N!}{(N-m)!} \approx N^m \)
  
  then \( P(m) = \frac{N^m}{m!} h^m e^{-Nh} \)
  
  on \( \quad \)
  
  \[ P(m) = \frac{(Nh)^m}{m!} e^{-Nh} \]
  
  Poisson distribution!

  Furthermore

  \[ Nh = \bar{m} \]
  
  average number observed in many trials.

  \[ P(m) = \frac{\bar{m}^m}{m!} e^{-\bar{m}} \]
Bernard Katz used this last form of the Poisson distribution to prove that:

1) each response to an action potential is made up of an integral number of units called "quanta".
2) the probability of a quanta being released is small, \( h \ll 1 \)
3) the number of quanta released is small, \( m \ll N \)

Katz had 198 responses (evoked)
- the average amplitude of a response was 0.933 mV
- the average amplitude of the spontaneous responses were 0.4 mV

\[ \bar{m} = \frac{0.933}{0.4} = 2.33 \]

They now applied the Poisson distribution to their data as follows:
\[ P(m) = \frac{m^m}{m!} e^{-m} \]

<table>
<thead>
<tr>
<th>m</th>
<th>obs</th>
<th>calculated</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>( P(0) = 198 \cdot e^{-2.33} = 19 )</td>
</tr>
<tr>
<td>1</td>
<td>44</td>
<td>( P(1) = 198 \cdot \frac{2.33}{1!} e^{-2.33} = 44 )</td>
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<tr>
<td>2</td>
<td>55</td>
<td>( P(2) = 198 \cdot \frac{2.33^2}{2!} e^{-2.33} = 52 )</td>
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<tr>
<td>3</td>
<td>36</td>
<td>( P(3) = 198 \cdot \frac{2.33^3}{3!} e^{-2.33} = 40 )</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>( P(4) = 198 \cdot \frac{2.33^4}{4!} e^{-2.33} = 24 )</td>
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