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INTERACTION BETWEEN INHIBITORY AND EXCITATORY SYNAPTIC POTENTIALS AT A PERIPHERAL NEURONE

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SUMMARY

1. The interaction between inhibitory and excitatory synaptic potentials in neurones lying in the submucous plexus of guinea-pig ileum has been examined.

2. It was found that during an inhibitory conductance change, electrotonic potentials were more depressed in amplitude than were excitatory synaptic potentials.

3. It is suggested that inhibitory conductance changes may have only a slight effect on the impedance seen by excitatory synaptic currents as much of the excitatory synaptic current flow is likely to be capacitive.

4. A part of the depression of excitatory synaptic potential amplitude was not associated with changes in electrical properties of neurones and it is suggested that inhibitory transmitter may reduce the release of excitatory transmitter.

INTRODUCTION

Inhibitory transmitter substances have been shown either to change the membrane properties of the post-synaptic cell (Brock, Coombs & Eccles, 1952; Smith, Wuerker & Frank, 1967) or to reduce the amount of transmitter released from excitatory nerve terminals (Dudel & Kuffler, 1961). It is often assumed that post-synaptic inhibitory action results from a reduction of the peak amplitude of the excitatory potential rather than from changes in membrane potential (Fatt & Katz, 1953; Ginsborg, 1967). However, at the synapses where the post-synaptic interaction between excitatory and inhibitory synaptic potentials have been examined, this interpretation is complicated by a variety of factors. For example, at the crayfish neuromuscular junction, inhibition is mediated both pre- and post-synaptically (Fatt & Katz, 1953; Dudel & Kuffler, 1961); the presynaptic action may well be dominant (Ginsborg, 1967). At central

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nervous system synapses the duration of inhibitory conductance change is often brief (Smith *et al.* 1967) and the distribution of excitatory synapses is complex (Jack, Miller, Porter & Redman, 1971).

In the submucous plexus of guinea-pigs, a proportion of neurones receive both excitatory and inhibitory synaptic inputs. The inhibitory synaptic potential is of long duration (several seconds) and produces a readily detectable change in cell input resistance, whereas the excitatory synaptic potential is relatively brief (about 50 msec) (Hirst & McKirdy, 1975). Analysis of the time course of decay of electrotonic potentials recorded from peripheral ganglia following the injection of small currents, has suggested that this may be described by a single exponential function (Martin & Pilar, 1963; McLachlan, 1974; M. E. Holman, personal communication). Moreover, attempts to determine soma to dendritic conductance ratio according to the method described by Rall (1959, 1960) have suggested that dendritic processes may make only a small contribution to cell conductance (Skok, 1973; McLachlan, 1974). It should be noted, however, that these experiments have depended on the use of single high resistance micro-electrodes to pass current and record changes in membrane potential. Nevertheless, it seems possible that an electrical description of ganglion cells may not be complex and that many of the complicating factors inherent in analyses of inhibition at other synapses might be absent in data obtained from neurones of the submucous plexus. The interaction between excitatory and inhibitory synaptic potentials has therefore been examined in this preparation.

METHODS

Preparations of submucous plexus were made from segments of mid-small intestine of guinea-pigs (females, 200–250 g) as described previously (Hirst & McKirdy, 1975). The strip of plexus (length ~1 cm, width ~5 mm) was pinned in an organ bath (see Hirst, Holman & Spence, 1974) with the mucosal surface downwards. The recording procedures, composition of physiological saline and bath perfusion system have been described (Hirst & McKirdy, 1975). However, in these experiments two separate pairs of transmural stimulating electrodes were used. Two fine platinum electrodes were inserted into the base of the organ bath; they were parallel to each other and separated by 5 mm. Two other platinum electrodes were placed over these, again parallel and 5 mm apart. Thus the preparation could be stimulated transmurally at two distinct points. Intracellular recordings were made from neurones in the part of the plexus strip which lay between the electrodes. The electrical properties of neurones were estimated by passing current through the recording electrode using a conventional preamplifier (W.P.I. instruments, M701). The method suggested by Martin & Pilar (1963) was used to correct 'bridge' balance.

Data were collected from neurones which had the appropriate synaptic input; that is those in which it was possible to evoke an inhibitory synaptic potential (i.s.p.) by transmural stimulation with one set of stimulating electrodes and a

single excitatory synaptic potential (e.s.p.) by transmural stimulation with the other set of electrodes. An e.s.p. was initiated once every two seconds throughout the duration of the experiment; just before or just after each e.s.p. a current pulse was passed through the recording electrode to determine the electrical properties of the impaled neurone. The i.s.p.s were initiated by applying a train of stimuli to the second pair of stimulating electrodes; the end of the train of inhibitory impulses preceded an e.s.p. by 0·4–0·8 sec. This sequence was repeated 30–40 times and the mean e.s.p. amplitude, cell input resistance and time constant, determined before, during and after the i.s.p.

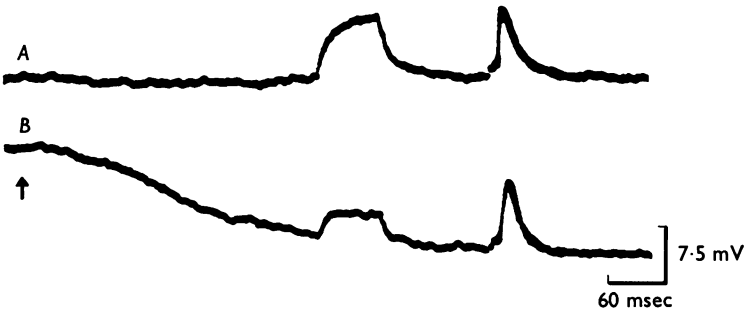

Fig. 1. Interaction between excitatory and inhibitory synaptic potentials. In each record an electrotonic potential is shown which was produced by passing a current pulse (approx. 5×10^{-10} A) through the recording electrode; following these e.s.p.s were evoked by transmural stimuli. When a train of impulses (20 Hz, 100 msec) was applied to the inhibitory nerve (at arrow), it can be seen that the membrane potential increased, the electronic potential was reduced in amplitude but that the peak amplitude of the e.s.p. was little affected. Calibration bars apply to both records.

RESULTS

Interaction between inhibitory and excitatory synaptic potentials. Excitatory synaptic potentials (e.s.p.s) and changes in membrane potential produced by passing current through the recording electrode (electrotonic potentials) were recorded. Stimulation of an inhibitory nerve caused an increase in membrane potential and a decrease in the amplitude of the electrotonic potential which lasted for some 4 or 5 sec (also see fig. 5, Hirst & McKirdy, 1975). However, the decrease in amplitude of the electrotonic potential was always greater than the decrease in e.s.p. amplitude. A typical experiment is shown in Fig. 1. The input resistance of this cell was about 190 MΩ; during the i.s.p. this fell to 90 MΩ. The control e.s.p. amplitude was 7·4 mV and during the i.s.p. this fell to 6·8 mV. In other experiments more intense inhibitory stimulation produced larger decreases in resistance but unless the cell resistance fell to less than 25% that of control the e.s.p. amplitude was not much affected (by less than 20%). According to conventional models (Fatt & Katz, 1953; Ginsborg, 1967) the apparent

failure of the i.s.p. to 'shunt' the e.s.p. could be explained either if the inhibitory conductance change was generated some distance from the cell soma or if the inhibitory potential change caused a large increase in the driving potential for the e.s.p. Both of these possibilities seem unlikely. The cell resistance was reduced during the i.s.p. (see Fig. 1); although the reversal potential for the e.s.p. is not known it seems unlikely that an increase of membrane potential of about 8 mV (see Fig. 1) could double the e.s.p. driving potential. In other peripheral

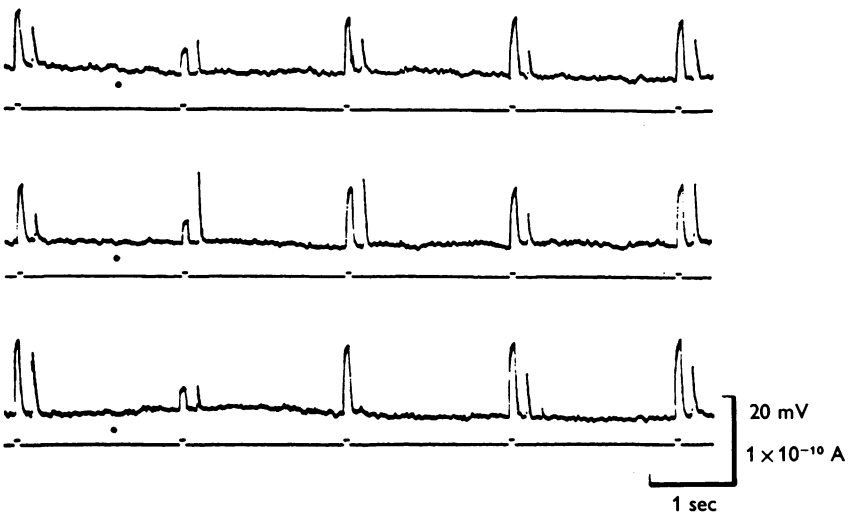

Fig. 2. Interaction between inhibitory and excitatory potentials recorded from a neurone whose resting potential had been increased to the reversal potential of the i.s.p. Inhibitory nerve stimulation (train duration 200 msec, 20 Hz, at arrow) produced a fall in cell resistance. It can be seen that in the third trace a transmural stimulus failed to initiate an e.s.p. 3 sec after the i.s.p.; this did not occur during control records. Calibration bars apply to each record.

ganglia the reversal potential is some 40–60 mV positive of resting membrane potential (Blackman, Ginsborg & Ray, 1963; Dennis, Harris & Kuffler, 1971); this is likely to be the case for neurones in the submucous plexus (G. D. S. Hirst, unpublished observations).

If the cell membrane potential is increased to the reversal potential of the i.s.p., activation of inhibitory synapses will produce no change in the driving potential of the e.s.p. but will change cell resistance. Consequently, to simplify the interpretation of results, in all subsequent experiments a steady hyperpolarizing current was passed through the recording electrode, the current intensity being adjusted to a value where inhibitory nerve stimulation produced no change in membrane

potential. Under these conditions, e.s.p. amplitudes were somewhat depressed during the inhibitory conductance change; the depression of peak amplitude of the e.s.p.s was still less than the depression of the amplitude of electrotonic potentials. It was also apparent that the depression lasted for longer than the change in electrical properties of the post-synaptic cell. Some of the records obtained during one experiment are shown in Fig. 2. It can be seen that the cell resistance had returned to control values after 4–5 sec. Since the amplitudes of successive e.s.p.s

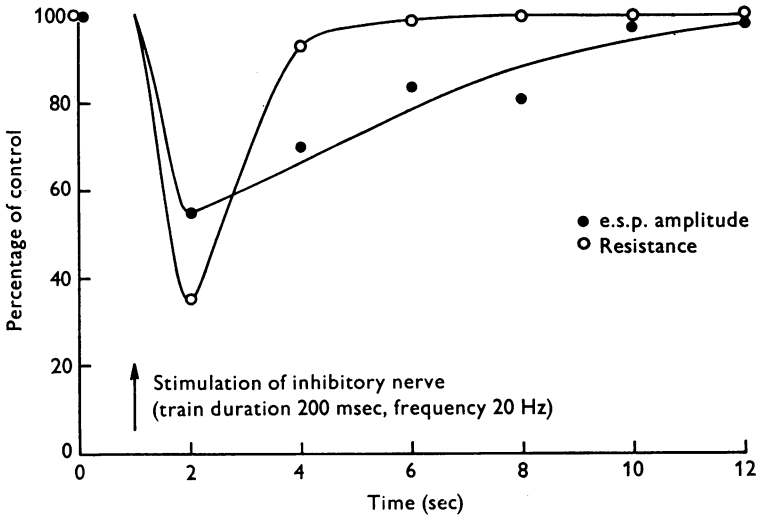

Fig. 3. Effect of inhibitory nerve stimulation of mean peak amplitude of e.s.p.s (filled circles) and on cell resistance (open circles) expressed as percentage of control. The control cell resistance was 190 MΩ, cell time constant 21 msec and control e.s.p. amplitude 8·2 mV. It can be seen that the cell resistance fell to approximately 30 % control whilst the e.s.p. amplitude had fallen to only approximately 50 % control. When a conductance change could no longer be detected the mean e.s.p. amplitude remained depressed for a further 4 sec. Each point is mean of thirty-six records.

fluctuated during each experiment, averages of up to forty records for each determination for each cell were made (see Methods). Typical values are shown in Fig. 3. In this experiment, the mean amplitude of the e.s.p. was still depressed some 4 sec after the input resistance had returned to its control level.

During the inhibitory conductance change the time course of e.s.p.s was faster. As shown in Fig. 4*A*, *B*, the time to peak potential was shortened and the rate of decay of potential more rapid. After the end

of inhibitory conductance change even though the e.s.p. amplitudes were depressed, their time course had returned to that of control e.s.p.s.

An increase in the intensity of inhibitory nerve stimulation led to a further depression of e.s.p. amplitude. In the experiment shown in Fig. 5 the train duration was kept constant (500 msec) and the stimulation frequencies were 10, 50 and 100 Hz. With less intense stimulation, the

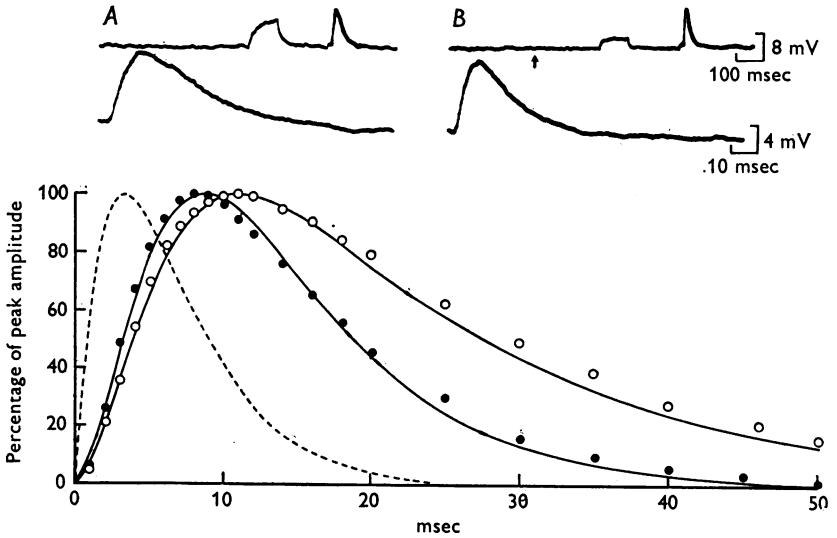

Fig. 4. Effect of inhibitory nerve stimulation on time course of e.s.p.s, recorded at reversal potential for i.s.p. *A* and *B* show control and 'shunted' records of electrotonic potentials and e.s.p.s respectively; lower traces show e.s.p.s recorded at faster sweep speed and higher amplification. After the inhibitory conductance change was over, but while the mean amplitude of e.s.p.s were still depressed, their time courses were identical to that shown in *A*. In *C* the time courses of e.s.p.s, before and during an inhibitory conductance change, expressed as a percentage of peak amplitude, have been plotted as open and filled circles respectively. The continuous lines show the time course of e.s.p.s computed on the assumptions that control cell resistance was 180 MΩ and fell to 80 MΩ during the i.s.p. and that the cell capacitance remained at 94 pF throughout. The dashed line shows the time course of synaptic current required to simulate both e.s.p.s. For further details see text.

initial depression of e.s.p. amplitude was not so marked and the return to control value more rapid; with higher frequency stimulation depression was more marked and prolonged. A somewhat similar depression of e.s.p. amplitude after an inhibitory conductance change has been demonstrated at the crayfish neuromuscular junction (Fatt & Katz, 1953) and results from a presynaptic action of the inhibitory transmitter (Dudel & Kuffler,

1961). Unfortunately we are unable to determine the statistical parameters that would describe the evoked release of excitatory transmitter as spontaneous excitatory synaptic potentials occur very infrequently and it is not known whether these are due to the release of individual quanta of transmitter. Furthermore, as these neurones have many excitatory inputs (Hirst & McKirdy, 1975) one cannot attribute those spontaneous

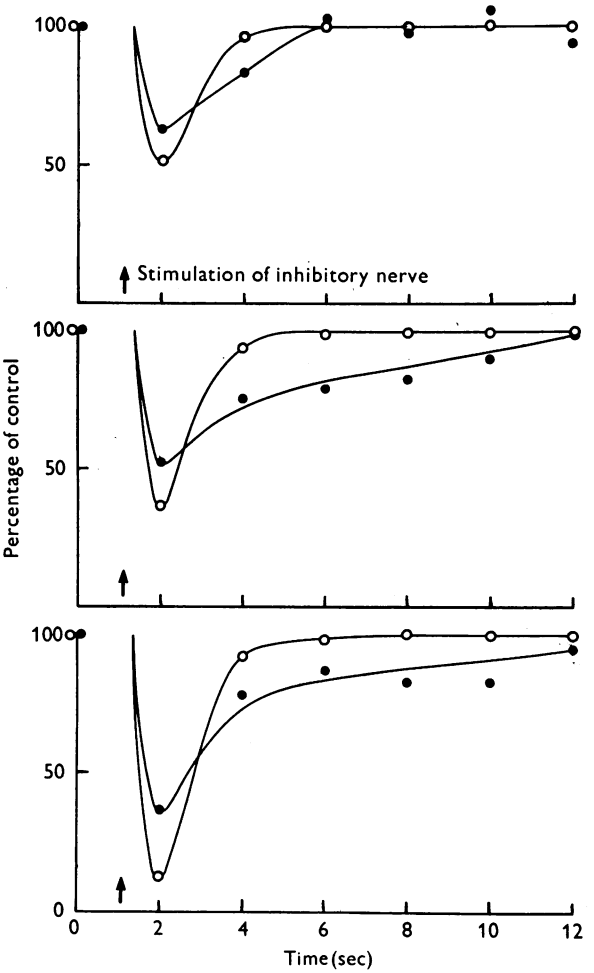

Fig. 5. Effect of varying intensity of inhibitory nerve stimulation on cell resistance (open circles) and mean amplitude of e.s.p.s (filled circles). In each experiment the train of impulses applied to the inhibitory nerve was of duration 50 msec. Stimulation frequencies were 10, 50 and 100 Hz in Figs. *A*, *B* and *C* respectively. Control input resistance of cell was 200 MΩ, cell capacitance 108 pF. Each point is the mean of between thirty-five and thirty-eight records.

potentials that do occur to the excitatory input being activated. However, it was a consistent observation that after the i.s.p. some excitatory stimuli failed to evoke a detectable e.s.p. This rarely occurred in the absence of inhibitory nerve stimulation and suggests that activation of inhibitory synapses can reduce the likelihood of excitatory transmitter release.

Effect of a change of cell resistance on excitatory synaptic potentials. Conductance models which only take into account cell resistance, predict that when the cell resistance is changed there will be approximately a proportional change in the e.s.p. amplitude unless the excitatory potential results from an intense conductance change. It can be seen that in our experiments (Figs. 3 and 5), the decrease in cell resistance was always greater than the decrease in e.s.p. amplitude despite some apparent presynaptic depression. An explanation for this could be that the impedance seen by the excitatory synaptic current was not much changed by the inhibitory shunt. If the excitatory conductance change is brief and the cell capacitance appreciable, much of the resulting excitatory synaptic current will flow 'across' that capacitance (see Gage & McBurney, 1973). Because neurones in this plexus have a high input resistance (60–250 MΩ) and a long time constant (13–27 msec) (Hirst & McKirdy, 1975; Hirst & Silinsky, 1975) even a relatively large change in cell resistance might only cause a small impedance change to synaptic currents. We attempted to test this possibility by computation.

Assuming that a neurone can be represented as a resistance (R) and a capacitance (C) in parallel, the membrane potential as a function of time, $V(t)$, resulting from flow of synaptic current $I(t)$ will be described by eq. (A 2) given in the Appendix. Where synaptic currents have been measured they can usually be described by the relationship

$$I(t) = At\, e^{-kt}, \tag{1}$$

where k is a constant and is the reciprocal of the time to the peak of the synaptic current (Jack & Redman, 1971) and A is a measure of the intensity of the peak synaptic current. Under these circumstances the synaptic potential is described by the relationship

$$V(t) = \frac{A}{C(1/RC-k)^2}[\{(1/RC-k)\,t-1\}\, e^{-kt} + e^{-t/RC}] + E_m, \tag{2}$$

where E_m is the resting membrane potential (see eqn. (A 5), Appendix).

The assumption that an excitatory synapse is a constant current generator is clearly an oversimplification. Excitatory transmitters produce conductance changes and the resulting currents are not independent of membrane potential (Ginsborg, 1967, 1973). However, in these experiments

even though the cell membrane potential was held at the reversal potential for the i.s.p., excitatory synaptic potential amplitudes were usually smaller than 10 mV. Therefore, the errors introduced by this simplification should be slight (see Appendix).

Values for input resistance, cell time constant and time to peak of the e.s.p. were determined experimentally in the absence of inhibitory nerve stimulation (Fig. 4*a*). Values for R and C were inserted into eqn. (2); k was varied until the computed peak voltage occurred at the same time as that determined experimentally. The entire time courses of the recorded and computed e.s.p.s were then compared (Fig. 4*C*). It can be seen that with a synaptic current of time to peak 3·3 msec, the agreement between predicted and experimental e.s.p.s is reasonable. In each of three experiments a similar time course of current gave an adequate description of the e.s.p. but the rising phase determined experimentally was faster than predicted whereas the measured decay was somewhat slower (see Fig. 4*C*). It may be that the synaptic current has a more complex form than described by our eqn. (1) (see for example, Martin & Pilar, 1963).

If one assumes that the inhibitory transmitter causes only a decrease in cell resistance (Fatt & Katz, 1953; Ginsborg, 1967) one may compute the time course of the 'shunted' e.s.p. In the experiment shown in Fig. 4*B* the input resistance fell to 80 MΩ (from 180 MΩ); cell capacitance and the time course of excitatory current were assumed not to change. It can be seen that the agreement between predicted and recorded e.s.p.s is again reasonable (Fig. 4*C*). Thus it seems that these neurones are adequately described as simple parallel resistance and capacitance circuits and that the excitatory synaptic current can approximately be described by a relatively simple equation (eqn. (1)).

This being the case one may use the relationship given in eqn. (2) to predict the relationship between cell input resistance and peak e.s.p. amplitude. The predicted relationship for a neurone of input resistance 200 MΩ, cell capacitance 108 pF is shown in Fig. 6 (continuous line). Fig. 6 also shows the relationships between e.s.p. amplitude and cell input resistance which are predicted by two models which neglect cell capacitance. The straight line (heavy dashes) assumes a constant synaptic current whereas the broken curved line was calculated from a conventional conductance model (Ginsborg, 1967). The mean amplitude of the e.s.p. was 7·5 mV and the driving potential assumed to be 70 mV. The experimental points shown in Fig. 6 are taken from the experiment shown in Fig. 5; this cell having the same values of resistance, capacitance and mean e.s.p. amplitude used in the calculations. It can be seen that for a variety of inhibitory 'shunts', the degree of depression of e.s.p.

amplitudes is not as great as would be predicted from a simple conductance model. It is however somewhat greater than would be predicted from our model incorporating cell capacitance. We feel that the most likely explanation for this discrepancy is that during the conductance change there is a concurrent depression of excitatory transmitter release.

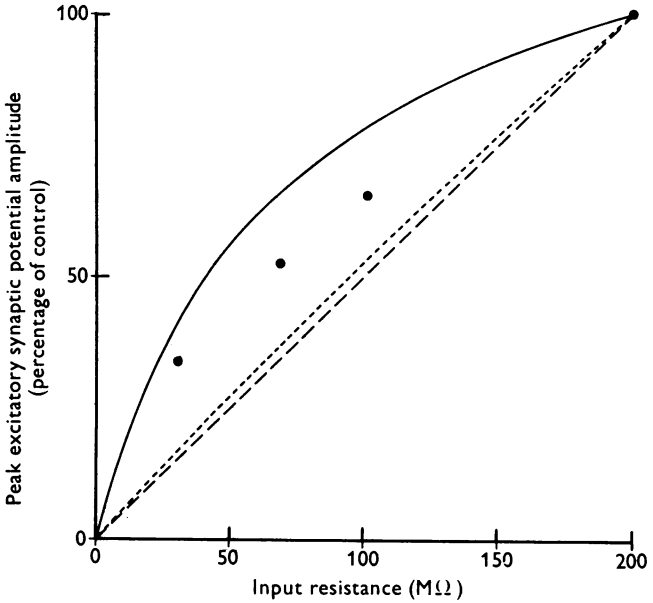

Fig. 6. Relationship between mean e.s.p. amplitude and cell resistance. Experimental points (filled circles) are taken from experiment shown in Fig. 5. The continuous line shows relationship between e.s.p. amplitude and cell resistance assuming that cell resistance was initially 200 MΩ, cell capacitance remained unchanged at 108 pF throughout and that the excitatory synaptic current remained unchanged throughout. The interrupted lines show relationships between e.s.p. amplitude and cell resistance calculated either on the assumption that excitatory synaptic current remained unchanged (heavy dashed line) or that it resulted from a resistive shunt of 1800 MΩ in series with a driving potential of 70 mV. In calculation of the latter relationships, the presence of cell capacitance was neglected. If it is assumed that the experimental points have been depressed by about 25 % of their values due to a presynaptic action of the inhibitory transmitter (see Fig. 4) scaling of the experimental points by this factor makes their values coincident with the continuous line.

DISCUSSION

Stimulation of inhibitory nerves produced a long-lasting depression of the mean amplitude of excitatory synaptic potentials if the post-synaptic membrane potential was held at the reversal potential of the

inhibitory transmitter. Only a part of this depression can be attributed to a change in the electrical properties of the post-synaptic membrane. That is, after an initial increase in membrane conductance with associated changes in e.s.p. time course, the membrane conductance returned to control values as did the time course of the e.s.p. time course. However, the mean amplitude of subsequent e.s.p.s remained depressed for several seconds. Though there are other explanations, it is likely that the inhibitory transmitter may depress the likelihood of release of excitatory transmitter. During the late depression of e.s.p. amplitude, many stimuli failed to evoke a detectable e.s.p. At some neuromuscular junctions in the crayfish and the crab, inhibitory nerve stimulation or application of the presumptive inhibitory transmitter causes presynaptic inhibition (Dudel & Ruffler, 1961; Parnas, Rahamimoff & Sarne, 1975). Recently we suggested that the catecholamines dopamine and noradrenaline could activate both inhibitory post-synaptic receptors and could cause a depression of the release of excitatory transmitter release at synapses in the submucous plexus (Hirst & Silinsky, 1975). If a related substance was released by the inhibitory presynaptic terminal it would not be surprising if inhibition was mediated by two mechanisms. Whether or not the presynaptic action is of physiological importance is not known; it will be appreciated that in these experiments i.s.p.s were generated by trains of stimuli and that insufficient transmitter may be released during low frequency activity to exert a presynaptic effect.

The interaction between i.s.p.s and e.s.p.s can be accounted for if it is assumed that the inhibitory transmitter causes an increase in membrane conductance (Fatt & Katz, 1953; Ginsborg, 1967). However, we suggest that only intense inhibitory conductance changes will appreciably change the impedance 'seen' by an excitatory synaptic current. The peak amplitudes of e.s.p.s recorded at the reversal potential of the i.s.p. were not depressed to the extent predicted from models which only take into account the resistive properties of cells. Moreover, our results suggest that at resting membrane potential, the impedance 'seen' by excitatory synaptic currents may be less affected during inhibitory conductance changes than is the driving potential for those currents increased. During intense inhibitory conductance changes, however, this balance may be reversed. An essential component of synaptic inhibition in these neurones is therefore the increase in membrane potential produced by the inhibitory transmitter. It should also be noted that the time course of excitatory synaptic current is somewhat slower than has been calculated for other synapses (Takeuchi & Takeuchi, 1959; Jack *et al.* 1971) but may not be much different to that of other peripheral ganglia (E. McLachlan, personal communication). As the excitatory synaptic current becomes progressively

briefer so the impedance 'seen' by that current will be less influenced by changes of cell resistance.

During the inhibitory conductance change, the time to peak potential was reduced and the decay of potential more rapid (see also Fatt & Katz, 1953). If the cell time constant is reduced, there will be a tendency for the time course of the synaptic potential to follow more closely that of the synaptic current. The peak potential will occur earlier and the potential decay more rapidly since charge on the membrane capacity may be more readily dissipated. A shortening of the duration of an excitatory synaptic potential will in itself be inhibitory if threshold is only reached after summation of two or more e.s.p.s except when e.s.p.s are generated synchronously.

Whenever two or more different, but not spatially distributed conductance changes interact, it is evident that one should consider the changed impedance of the cell rather than the changed resistance of the cell which results from one of conductance changes. Since excitatory conductance changes are usually brief compared with cell time constants, much of the resulting synaptic current flow will be capacitive. A change in cell resistance will change the proportions of resistive and capacitive current in a complex manner but almost invariably the change in cell resistance will exceed the change in impedance seen by excitatory synaptic currents. However, it is to be stressed that when the conductance changes are spatially distributed a more complex analysis would be required.

APPENDIX

Calculation of the time course of excitatory synaptic potentials.

(i) Calculated on the assumption that an excitatory synapse may be described as a constant current generator. At node X, the algebraic sum of currents at any time t must equal zero (Fig. 7A):

$$i_1+i_2+i_3 = 0. \tag{A 1}$$

If the current source has a time course $I(t)$ then substituting in eqn. (A 1), gives a solution for voltage, $v(t)$, between the inside and outside of the cell,

$$(v(t)-E_m)/R+C\mathrm{d}v(t)/\mathrm{d}t-I(t) = 0, \tag{A 2}$$

where R and C are the cell input resistance and cell capacity respectively, E_m is the cell resting potential and A is a measure of the current intensity. Where synaptic currents have been measured they can often be described by the relationship

$$I(t) = At \exp(-kt),$$

where k is the reciprocal of time to peak current (for justification see Jack & Redman, 1971). Substituting in eqn. (A 2)

$$(v(t)-E_m)/R+C\,\mathrm{d}v(t)/\mathrm{d}t-At\exp(-kt)=0.$$

Rearranging

$$\mathrm{d}v(t)/\mathrm{d}t+v(t)/RC = At\exp(-kt)/C+E_m/RC. \qquad \text{(A 3)}$$

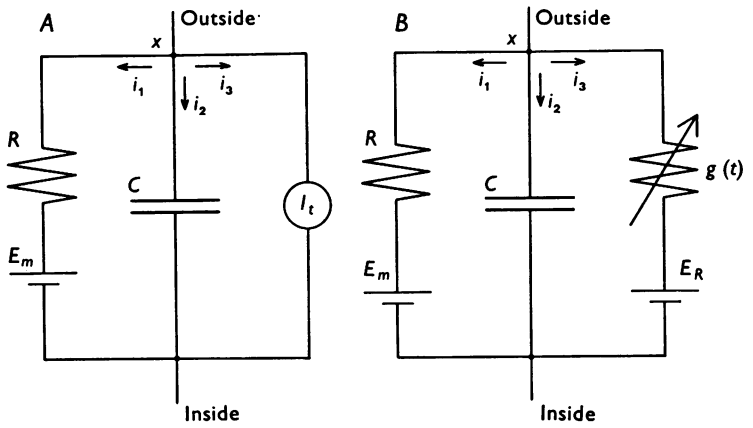

Fig. 7. Simplified equivalent circuits for action of transmitter. In A the excitatory synapse is represented as a constant current generator of infinite resistance which generates a current, I_t. Some of the current is assumed to flow through the cell resistance (R) and some to discharge the membrane capacity (C). The cell resting potential is represented by E_m. In B, synaptic current is assumed to result from a conductance change $g(t)$, in series with a battery E_R which represents the reversal potential of the transmitter.

Multiplying both sides by the integrating factor $\exp(t/RC)$

$$\mathrm{d}/\mathrm{d}t[v(t)\exp(t/RC)] = \frac{At}{C}\exp[t(1/RC-k)]+\frac{E_m}{RC}\exp(t/RC).$$

After integration

$$v(t)\exp(t/RC) = \frac{A}{C}\int_0^t \mathrm{T}\exp[\mathrm{T}(1/RC-k)]\,\mathrm{dT}+\frac{E_m}{RC}\int_0^t \exp(\mathrm{T}/RC)\,\mathrm{dT}+K,$$

where K is a constant and depends on initial conditions and where T is a measure of time and is introduced for the purposes of integration.

$$v(t)\exp(t/RC) = \frac{A}{C}\left[\frac{\mathrm{T}\exp[\mathrm{T}(1/RC-k)]}{1/RC-k}-\frac{\exp[\mathrm{T}(1/RC-k)]}{(1/RC-k)^2}\right]_0^t$$

$$+\frac{E_m}{RC}.RC[\exp(\mathrm{T}/RC)]_0^t+K.$$

After substitution of integration limits and further rearrangement:

$$v(t) = \frac{A}{C(1/RC-k)^2}\left[\left\{(1/RC-k)\,t-1\right\}\exp(-kt)+\exp(-t/RC)\right] + E_m[1-\exp(-t/RC)]+K\exp(-t/RC). \quad \text{(A 4)}$$

At zero time, $t = 0$, $v(t) = E_m$. Substituting into eqn. (A 4) gives

$$K = E_m,$$

$$v(t) = \frac{A}{C(1/RC-k)^2}\left[\left\{(1/RC-k)\,t-1\right\}\exp(-kt)+\exp(-t/RC)\right]+E_m. \quad \text{(A 5)}$$

This result was verified by analysis using Laplace transforms and was used to compute the time course of e.s.p. for experimental results. A

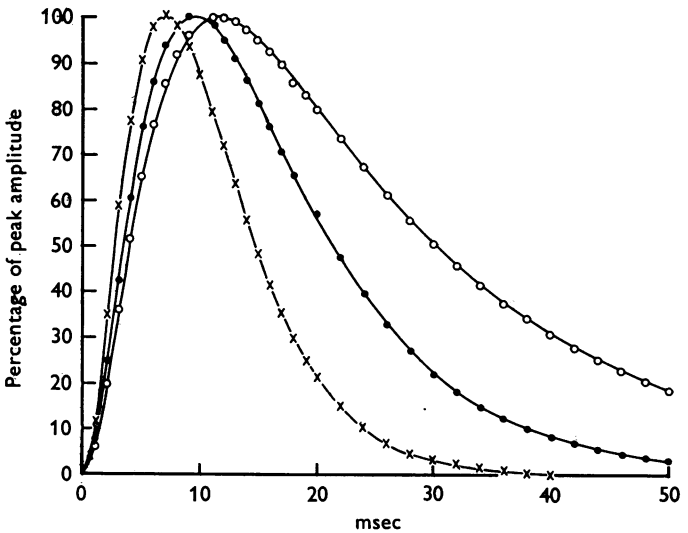

Fig. 8. Comparison between the time courses of e.s.p.s simulated either by constant current injection or by a conductance change. The continuous lines were computed for idealized cell of initial resistance 200 MΩ and during inhibitory conductance changes which reduced the cell resistance to 100 and 40 MΩ; the cell capacitance was taken to be 100 pF throughout. It was assumed that the synaptic current (I_t) had a time course of the form $I(_t) = t\,e^{-kt}$, where k had a value of 300 (i.e. time to peak current 3·3 msec). The open circles, filled circles and crosses show the time courses of e.s.p.s generated under similar conditions when the synaptic current resulted from a conductance modulation, $g(t)$. The time course of the conductance modulation was assumed to have the form $g(t) = t\,e^{-kt}$ with a peak shunt of 500 MΩ occurring 3·3 msec after the onset of modulation. The driving potential (i.e. $R_E - R_M$) was assumed to be −70 mV so generating an e.s.p. of peak amplitude 7·4 mV for the idealized cell (R = 200 MΩ, C = 100 pF).

series of solutions for an idealized cell are shown in Fig. 8, where the time courses of e.s.p.s generated for changing values of R are shown.

(ii) Calculated on the assumption that a synaptic potential results from an increased conductance to one or more ions.

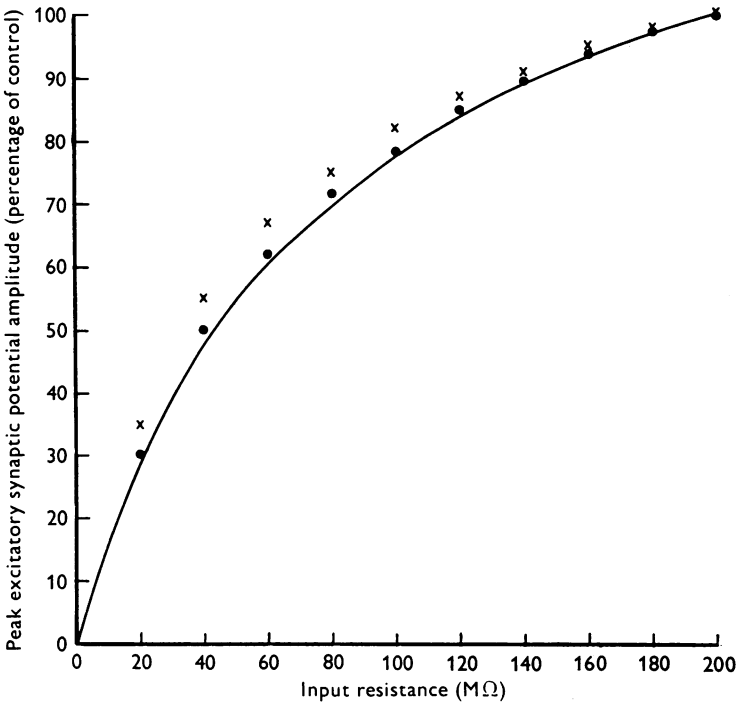

Fig. 9. Comparison of the relationships between peak e.s.p. amplitude and cell resistance computed for e.s.p. generated by constant current and conductance modulation models. The values of R and C and k are as shown in Fig. 8. Continuous line shows the relationship predicted by the constant current model. The filled circles and crosses are the predicted relationships from conductance modulations of peak values 500 and 200 MΩ respectively. Only as the excitatory conductance modulation becomes intense is there a marked deviation between the models; this is especially apparent at low values of R.

The more realistic model for the generation of a synaptic potential is shown in Fig. 7*B*. Again at node X

$$i_1+i_2+i_3 = 0,$$

$$\mathrm{d}v(t)/\mathrm{d}t+\frac{g(t)+1/R}{C}\,v(t) = \frac{E_m/R+E_R\,g(t)}{C}, \qquad \text{(A 6)}$$

where $g(t)$ is the conductance of the 'synaptic channel' at time t, E_m and E_R are the resting membrane potential and the reversal potential of the

transmitter respectively. Solving eqn. (A 6) as previously gives the general solution for $v(t)$ arising from any conductance transient, $g(t)$.

$$v(t) = \frac{1}{C}\int_0^t [E_m/R + E_R\, g(\mathrm{T})].\ \exp\left[-\int_{\mathrm{T}}^t \frac{g(x)+1/R}{C}\,\mathrm{d}x\right]\mathrm{dT} + E_m \exp\left[-\int_0^t \frac{g(x)+1/R}{C}\,\mathrm{d}x\right]. \quad \text{(A 7)}$$

For a step of conductance change (Gs)

$$g(t) = \begin{cases} 0 & t < 0 \\ Gs & t \geqslant 0. \end{cases}$$

Substituting this function into eqn. (A 7) gives

$$v(t) = \frac{E_m/R + E_R\, Gs}{1/R + Gs}\left[1 - \exp\left(-\frac{Gs+1/R}{C}\,t\right)\right] + E_m \exp\left(-\frac{Gs+1/R}{C}\,t\right).$$

After rearrangement this equation agrees precisely with that derived by Ginsborg (1973) for the same conditions.

If one assumes that the conductance modulation has the same form as a synaptic current which generates a small synaptic potential, i.e $g(t) = At\,\mathrm{e}^{-kt}$, where A is a measure of the intensity of modulation and k is the reciprocal of time to peak conductance, substituting into eqn. (A 7) yields the expression for $v(t)$. It is to be stressed that this does not imply that $I(t)$ will now have a similar time course under all conditions but will depend upon the intensity of conductance modulation.

$$v(t) = \frac{E_m}{RC}E(t)\int_0^t \exp\left[\frac{\mathrm{T}}{RC} - \frac{A}{kC}\,\mathrm{T}\,\mathrm{e}^{-k\mathrm{T}} - \frac{A}{k^2C}\,\mathrm{e}^{-k\mathrm{T}}\right]\mathrm{dT} + \frac{AE_R}{C}E(t)\int_0^t \mathrm{T}\exp\left[(1/RC - k)\,\mathrm{T} - \frac{A}{kC}\,\mathrm{T}\,\mathrm{e}^{-k\mathrm{T}} - \frac{A}{k^2C}\,\mathrm{e}^{-k\mathrm{T}}\right]\mathrm{dT} + E_m\,E(t)\exp\left(-A/kC^2\right), \quad \text{(A 8)}$$

where

$$E(t) = \exp\left[\frac{A}{kC}\,t\,\mathrm{e}^{-kt} + \frac{A}{k^2C}\,\mathrm{e}^{-kt} - t/RC\right].$$

Further reduction of this expression is difficult; numerical solutions were obtained by use of a computer.

A comparison between the time courses of e.s.p.s generated by either model is shown in Fig. 8. It can be seen that when the e.s.p. results from a small intensity conductance modulation there is little difference between the solutions. Moreover, the relationship between peak e.s.p. amplitude and cell resistance is little affected unless the excitatory shunt is intense (Fig. 9).

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