DENDRITIC LOCATION OF SYNAPSES AND POSSIBLE MECHANISMS FOR THE MONOSYNAPTIC EPSP IN MOTONEURONS

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The purpose of this paper is to bring together recent experimental and theoretical results which, when considered together, add to our understanding of the monosynaptic excitatory postsynaptic potential (EPSP) in motoneurons. A general mathematical neuron model has been proposed which provides a means of computing EPSP properties that result when synapses are distributed over the soma and dendrites of a nerve cell (29). This general model contains a set of theoretical parameters corresponding to such neuronal properties as the membrane time constant, the dendritic electrotonic length, the surface area ratio and the conductance ratio of dendrites to soma, the spatial distribution of synaptic input over the soma-dendritic surface, and the time course of synaptic current or synaptic conductance. Every specific application of this general model depends upon selecting a set of values for these parameters. We wish to explore the application of this general model to the particular case of the cat spinal motoneuron. Intracellular recordings from motoneurons have provided a description of many of the properties of the monosynaptic EPSP's of these cells (4, 7, 8, 24, 32). In particular, the shapes of the unitary, miniature EPSP's resulting from activation of single Ia afferent fibers have been described. The relationship of these unitary EPSP's to the composite EPSP's elicited by electrical stimulation of many Ia fibers has been discussed (4).

We wish to determine whether the experimental data will allow us to put some restrictions on the model parameters which determine EPSP shapes and to provide a more sharply defined picture of the organization of synapses on the motoneuronal soma and dendritic tree.

In Part I of this paper we will show that a number of restrictions do emerge from the analysis. For example, we have found that simple variations in the time course of synaptic currents cannot reproduce the observed EPSP shapes if the synaptic input is distributed uniformly over the motoneuron surface. The most restrictive model which successfully simulates the observed data, and the model which we will discuss in some detail, involves a single time course for the synaptic current, but with the synaptic input occurring in different combinations of somatic and dendritic locations. Thus, a
relatively restrictive model composed of functionally identical synapses distributed to various somatic and dendritic loci is sufficient to explain the experimental data. Since this, of course, does not prove that this restrictive model in fact corresponds in detail to the physiological situation, a number of alternative versions of the general model will be explored in this paper.

In Part II of this paper we will examine the electrophysiological observations on the monosynaptic EPSP reported in the earlier papers of this series (4, 24, 32) in relation to the conceptual model of synaptic inputs distributed over the neuronal soma and dendrites. Particular attention will be given to the kinds of conclusions that can and cannot be drawn about possible membrane mechanisms underlying the generation of the EPSP.

Assumptions

Here are stated the assumptions underlying the treatment of the observations to follow. We believe these assumptions can be accepted as reasonable.

EPSP recording site. It is assumed that the intracellular recordings to be discussed here were obtained from sites in or near the motoneuron somata.

Location of synapses. It is known that synaptic structures are distributed over the entire surface of the motoneuron soma and dendrites (14, 30, 33, 34). We assume that the synapses generating monosynaptic EPSP’s may also be widely distributed.

Synaptic current. It is assumed that each active synaptic ending produces a brief flow of electric current inward across the subsynaptic region of the motoneuron membrane and this current has a depolarizing effect upon the motoneuron membrane. No assumption is necessary at this point as to the mechanism of the generation of this synaptic current; this question is deferred to Part II of this paper.

The theoretical computations incorporate the notion that the electrotonic extent of motoneuron dendritic trees can be approximated by an equivalent cylinder or a chain of compartments (27, 28). For most of the computations in this paper the electrotonic distance from the soma to the dendritic periphery was assumed to be 1.8 times the characteristic length constant, \( \lambda \), of the equivalent cylinder. Additionally, in order to compare the computed EPSP shapes with those observed experimentally, it is necessary to choose some value for the passive membrane time constant, \( \tau \). A value of 5 msec was used for most of the comparisons. These choices will be examined in some detail below.

Part I: Effects of Spatial Distribution of Synaptic Input Upon EPSP Shape and Upon Certain EPSP Properties

In this section we wish to compare the shapes of various computed EPSP’s with the range of EPSP shapes observed electrophysiologically. The different computed EPSP shapes were obtained by varying synaptic input location, the duration of the synaptic current, or both, in a mathematical neuronal model system. The shapes of these computed EPSP’s will be com-
pared with the shapes of the "miniature EPSP's" or unitary synaptic potentials discussed in an earlier paper (4). These miniature EPSP's are elicited by activity in single Ia afferent fibers (5) and are apparently composed of smaller subunits or "quantal EPSP's" (20) which arise at single synaptic endings. After this we will deal with the problem of the "evoked" EPSP, i.e., the monosynaptic EPSP produced by synchronous stimulation of a population of afferent fibers and therefore composed of a number of miniature EPSP's.

EPSP SHAPE INDICES

We have used two quantitative shape indices in comparing the shape of the calculated and experimental EPSP's.

1. **Time to peak.** This is defined as the time from the foot to the peak of the EPSP. For the computed EPSP's the foot is defined as the point of intersection with the base line of a line drawn through the two points on the rising phase when the EPSP attains 10% and 50% of its peak amplitude. The foot or onset of the experimental EPSP's is defined by inspection as the earliest deflection of the PSP above the base line. In practice, these methods of defining the time to peak are closely similar.

2. **Half-width.** This is defined as the duration of the EPSP measured between the points on the rising and falling phases which are one-half the peak amplitude (cf. Fig. 1, arrows).

A number of the other indices of EPSP waveform, e.g., the maximum rate of rise of the EPSP divided by its maximum amplitude, were highly correlated with these two shape indices (24, 29).

UNIFORMLY DISTRIBUTED SYNAPTIC INPUT

When synaptic input is distributed equally to all regions of a neuronal model, both EPSP generation and decay are the same in all regions and there is no electrotonic spread between regions. The case of uniformly distributed synaptic input is therefore favorable for examining the effects on EPSP shape indices of varying the time course of synaptic current in the absence of any complicating factors related to synaptic location. The right-hand part of Fig. 1 shows three computed EPSP's (solid traces) generated by the corresponding synaptic currents (dotted traces).

The time course of these synaptic currents was defined by

\[ \text{F}(t) \propto e^{-t/t_p} \]

where \( t \) represents time as a variable starting from zero, and \( t_p \) is a constant to be selected; the value of \( t_p \) is equal to the time when this input transient reaches its peak value. For the "fast" transient (top right, marked with a diamond) \( t_p = \tau /50 \); this means that \( t_p = 0.1 \) msec for \( \tau = 5 \) msec. In the case of the "slow" transient (lower right, marked with a square) \( t_p = \tau /10.9 \), corresponding to \( t_p = 0.46 \) msec when \( \tau = 5 \) msec. For the "medium" transient (triangle) \( t_p = \tau /25 \), corresponding to \( t_p = 0.2 \) msec for \( \tau = 5 \) msec.

The slower synaptic currents produce EPSP's with the expected increase in time to peak and half-width. These shape indices are plotted on the graph.
on the left of Fig. 1. Time to peak is plotted as the abscissa and the half-width (labeled "duration at 1/2 amplitude") as the ordinate.

The shape indices of the fast, medium, and slow EPSP's are represented by the diamond, triangle, and square, respectively. After the active synaptic current is completed, the EPSP decay is a simple exponential with a time constant that is equal to the passive membrane time constant \( \tau \). In particular, for increasingly brief synaptic currents, the limiting value for the half-width as the time to peak approaches zero, must be simply the half-time for exponential decay, defined as

\[
t_{1/2} = 0.693 \tau
\]

This limiting value provides the ordinate intercept of the solid line in Fig. 1 which passes through the other plotted points. This line corresponds to the locus of shape indices of EPSP's which are generated by synaptic currents of varying duration and with uniform distribution over the cell surface (no electrotonic spread of current within the cell occurs in this situation). The line in the graph of Fig. 1 provides a useful reference and will appear on subsequent plots.

**Localized Synaptic Input**

When synaptic input occurs to restricted regions of the neuron, results are obtained which are quite different than is the case with uniformly dis-
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tributed input. The right half of Fig. 2 presents a diagrammatic summary of the computational model which has been used to analyze the consequences of localized synaptic input; a more detailed treatment of the computational model is available elsewhere (28, 29). The inset diagram in the upper right of Fig. 2 provides a schematic reminder of how the extended receptive surface of certain neurons, including motoneurons, can be represented as a chain of

Fig. 2. Right: diagrammatic representation of the transformation of soma-dendritic receptive surface of a neuron into a chain of 10 equal compartments. Below this are graphs of computed EPSP's occurring in compartment 1, obtained with the compartmental model for the medium synaptic current time course (upper graph, dotted line). Synaptic current introduced equally to all compartments gave the upper computed EPSP (solid triangle). Synaptic current localized to a single compartment gave the lower computed EPSP's. Compartment 1 (open triangle, 1), compartment 4 (open triangle, 4), or compartment 8 (open triangle, 8). Left: a plot of EPSP shape index values for computed EPSP's shown at right. Dashed line gives locus of EPSP shapes generated when synaptic input is limited to the numbered compartment. Solid line represents cases of uniform depolarization of the cell. Discussion in text. Note that scales are in units of dimensionless ratio $t/\tau$.

10 compartments. Each compartment represents an equal amount of membrane surface area. The neuron soma is represented by compartment 1, while compartment 10 represents a lumping of the most peripheral portions of all the dendritic trees. Compartments 2 through 9, then, represent divisions of equal electrotonic distance, beginning with the dendritic trunks and extending to the dendritic periphery.

The two graphs on the lower right of Fig. 2 show computed EPSP's which have been discussed in the previous paper (29). A brief duration of synaptic current was assumed and this is shown in the dotted curve of the middle right
figure. The single EPSP shown in the middle inset (solid triangle) illustrates the predicted shape when synaptic input is distributed equally to all 10 compartments, and is the same as the middle trace of Fig. 1. The lowermost inset on the right displays 3 different EPSP shapes predicted to occur in compartment 1 (as would be observed with a microelectrode inside the soma) for 3 cases of localized synaptic input each generating synaptic current with the same time course but of differing magnitudes. The slowest EPSP (triangle 8) was obtained when synaptic input was localized to compartment 8; the fastest (triangle 1) occurred with input localized to compartment 1, and the intermediate shape (triangle 4) was produced by input localized to compartment 4.

The left side of Fig. 2 presents a plot of the EPSP shape indices defined earlier. Each open triangle plots the shape index values of a computed EPSP, as seen in compartment 1, when synaptic input was localized to the compartment number designated within the triangle. These shape indices were obtained from calculated EPSP’s such as shown in the lower right inset. The dashed line drawn through the open triangles illustrates how the shape indices increase as the localized synaptic input is shifted from the soma toward distal dendritic regions. With inputs in compartments 1 through 6, there is an almost direct proportionality between the PSP half-width and the time to peak; the half-width is very close to three times the corresponding time to peak. For synaptic inputs in the distal compartments, however, the half-width values fail to increase proportionately with the time-to-peak values.

Effect of electrotonic spread. The trend of the change in the EPSP shapes summarized by the dashed line in Fig. 2 can be grasped intuitively in terms of electrotonic spread of membrane depolarizations away from the location which receives the synaptic input. This is facilitated by comparison of the dashed line with the solid line which represents the case of uniformly distributed input (as in Fig. 1). The solid triangle on this graph corresponds to the uniformly distributed case with a synaptic current identical with that of the open triangles.

The faster EPSP shapes correspond to synaptic input locations in the proximal half of the soma-dendritic chain of compartments and, in these cases, electrotonic spread is directed primarily away from the soma, sharpening the PSP peak and causing the early falling phase of the potential to decay faster than would a uniformly distributed depolarization. In the cases where synaptic input is located in the distal half of the chain, electrotonic spread takes place largely toward the soma with appreciable delay between the time of occurrence of the distal current transient and the voltage transient in compartment 1. Also the EPSP is more rounded and the early falling phase is slower than for a uniformly distributed depolarization. These factors account for the longer half-width values for the distally generated EPSP’s. It is worth noting that the solid line, representing uniformly distributed synaptic input, intersects the dashed line at a point between the points for EPSP’s generated in compartments 5 and 6, thus separating the PSP shapes obtained with in-
put locations in the proximal one-half of the soma-dendritic chain from those generated for input locations in the distal one-half of the chain.

Before the computed EPSP shapes of the sort illustrated in Figs. 1 and 2 can be compared with experimentally observed miniature EPSP's, it is necessary to use a particular value for the passive membrane time constant, \( \tau \), in order to convert the dimensionless scale of the computation, \( t/\tau \), into a scale in msec. Because \( \tau \) is a membrane parameter that cannot be directly measured in motoneurons, its value must be estimated from a

matching of theoretically and experimentally recorded transients in motoneurons (26). Observation on motoneurons have provided such estimates, with typical \( \tau \) values around 5 msec, but with values near 7 msec occurring not uncommonly (10, 16, 22, 26).

Figure 3 displays shape index plots for individual experimental miniature EPSP's (on the left) from 11 sets of rhythmically occurring PSP's identified as arising from group Ia afferent fibers, and in the right-hand plot the shape indices of electrically evoked EPSP's (the population responses) obtained from 7 of the same cells from which miniature synaptic potential data were collected. The variation in the shape indices of the EPSP's arising from a particular fiber is relatively limited, but the variation tends to increase with increasing value of the indices. The scatter pattern of the plotted shape in-
indices, viewed as a whole, appears as a continuum of values from the minimum (1678A) to maximum (1633C and 1707A). The plot includes two reference lines from theoretical computations. The dashed line is the locus of shape indices of computed EPSP's with input localized to a single compartment. The time course of synaptic current used in computing this curve was the fast current transient (●) of Fig. 1, with $t_\tau = \tau/50$. This synaptic current duration produces calculated EPSP's which are in good agreement with the 0.3 msec minimum time-to-peak value of observed miniature EPSP's (cf. 4). The solid line is the locus of shape indices where the synaptic input is equal in all compartments (as in Fig. 1). Three conclusions are evident from this plot: 1) the slope which can be envisioned for the scatter of observed EPSP measurements departs from the slope of the linear portion of the dashed line (localized input case) but the faster miniature EPSP measurements do scatter around the lower end of the theoretical line; 2) there is an increasingly greater departure of observed shape indices from the dashed line with increasing duration of time-to-peak and half-width values. The experimental miniature EPSP's have shorter times to peak and longer half-widths than would be expected if they represented localized inputs to increasingly distant dendritic compartments; 3) the solid line, which represents the case of simple variations of the synaptic current time course with a uniformly distributed synaptic input provides a very poor match with the experimental data.

On the right in Fig. 3 the shape indices for evoked EPSP's are plotted for those cells in the series for which data was available (cf. 4). It is rather striking that these measurements scatter along the same slope as do the values for the miniature EPSP's, being almost exactly midway between the extremes of both time-to-peak and half-width values. This characteristic of the evoked EPSP agrees with the notion already proposed (4) that the wave shape of the evoked EPSP represents the summation of a wide spectrum of miniature EPSP shapes which make up the larger potential (see below). The theoretical reference lines are again as described above.

The disparity between the observed shape indices of experimental miniature EPSP's and those of calculated EPSP's with localized input (dashed line) was initially unexpected since our first assumption was that miniature EPSP's would arise in more or less localized electrotonic regions of the motorneurons. The miniature EPSP's with the longest half-widths are thus far unaccounted for, making it desirable to explore the consequences of various assumptions as to synaptic input location and time course which might yield potentials with shorter time-to-peak values for longer half-width values. The discussion to follow will deal with such computations together with the intuitive notions which have emerged from these attempts.

Effects of synaptic current time course. For the case of equal synaptic input to all compartments, the effect of changing from medium to fast or slow synaptic current time course (Fig. 1) is of very little help in accounting for the experimental range of Fig. 3. It seemed worthwhile, however, to explore the results of changing the synaptic current time course in single compartments.
of the model. In Fig. 4 are shown the results of this procedure. The dotted outline shows the range of experimental EPSP shape indices plotted in detail in Fig. 3. The lower limit to synaptic current duration appears to be near 0.3–0.4 msec as judged by the fastest miniature EPSP's (4) and the open diamonds in Fig. 4 correspond to computed EPSP's generated by synaptic currents with this time course. Each diamond plots the shape indices for the EPSP which would occur at the soma when this fast synaptic current occurs in the compartment numbered in each diamond. The squares are a similar locus of points for a slow synaptic current. These synaptic currents, in fact, correspond to currents labeled with the diamond and square in the right upper and lower insets of Fig. 1. It is clear from Fig. 4 that the fast current produces the closest fit to the data and lengthening the synaptic currents in any one compartment tends to increase the discrepancy between observed and calculated shape indices.

**Combinations of input locations.** We have explored the varieties of EPSP shapes that can be obtained by using combinations of two or more input locations. When these inputs were permitted to have different time courses, it proved easy to find input combinations that resulted in computed EPSP shapes with the required large half-width/time-to-peak ratios. Fast and proximal inputs tend to shorten the time to peak, while slow and distal inputs tend to lengthen the half-width. In fact, extreme combinations can result in computed shapes with two peaks, an early peak and a late peak; these were excluded from the present study. Two more moderate examples of such computed EPSP shapes are plotted as X and Y in Fig. 4. The EPSP shape
plotted as \( X \) was obtained with medium duration synaptic input to compartment 3, plus a slow input to compartments 8, 9, and 10. The peak amplitude of synaptic current at the proximal location was three times that in each of the distal compartments. This combination of parameters clearly produces an EPSP matching the observed EPSP’s with long half-widths which had not been matched by the procedure discussed earlier. It is remarkable that when the proximal input was shifted from compartment 3 to 4 (and the peak amplitude of the proximal input was raised to four times that in each distal compartment), the time to peak was more than doubled. The shape indices of the resultant EPSP are plotted as point \( Y \). Points \( X \) and \( Y \) are two examples of computed results which indicate that a combination of different synaptic current time courses and different input locations can produce a good match with the experimental data.

A reasonable, simplifying assumption is that the time course of synaptic current is similar at all the terminal boutons of Ia fibers. All miniature EPSP’s considered in the present paper were generated as a consequence of activity in single Ia afferent fibers (5). Thus, the slow time course of synaptic currents used above in compartments 8, 9, and 10 would imply some temporal dispersion in the occurrence of the synaptic currents at the individual boutons which are connected to a single Ia fiber. This dispersion could result from one of two causes: 1) variations in the time of depolarizations of the different end knobs associated with a single fiber (17), and 2) variation in the time of generation of the synaptic current after depolarization of the endings has occurred (synaptic delay) (18). Observations on electrically evoked unitary miniature EPSP’s in motoneurons indicate a reasonable maximum would be about 1 msec for such temporal dispersion in motoneurons (4, 5, 20).

**Multiple input locations with single input time course.** It would be a considerable restriction on the model if a match with the experimental data could be obtained with changes in only one of the model parameters, input location, or current time course. We have seen that limited variations in current time course alone will not produce such a match. Figure 5, however, shows that various combinations of input locations can produce a close match of the experimental data, utilizing only a single time course of the synaptic current in the different input locations. The experimental points are shown as small open circles, and the triangles and diamonds correspond to various computed EPSP’s. The inputs used to generate these EPSP shapes all combine localized input in both proximal and distal compartments, with varying intensity or “weight” in the different locations. These trials used identical synaptic current durations at the proximal and distal locations; these are denoted by the diamond and triangle points labeled \( A \), \( B \), and \( C \). The PSP’s plotted as diamonds were obtained with the fast input transient \((t_p = \tau/50)\), which, in the pure localized case, generated the points on the dashed reference line. The triangles denote PSP’s produced with the medium duration input \((t_p = \tau/25)\). In both of these series, \( A \) designates the EPSP shape when synaptic input is located in both compartments 1 and 2 and in 9 and 10 simultaneously, with the distal input intensity twice as large as that in the proximal compartments. Compared with proximal input alone, these results show a significant increase of half-width with little change in time to
peak. The shapes designated \( B \) were obtained as in \( A \), but with an additional input to compartments 3 and 4 in the same amount as the input in 1 and 2. This results in a small increase in both time to peak and half-width. A striking change in shape occurs \( (C) \) when the input to compartments 1 and 2 is deleted, leaving that to compartments 3 and 4 plus 9 and 10 the same as in \( B \). Here we obtain half-width values nearly as large as with distal input alone, but with considerably shorter time-to-peak values.

These combinations of synaptic input locations have been utilized in attempting to match the experimentally observed EPSP’s resulting from activity in single Ia afferent fibers. Wide distribution of the synaptic endings from a single fiber is thus implied by this means of explaining the results.

**Fig. 5.** Shape index plot of half-width \((\text{ordinate})\) versus time to peak \((\text{abscissa})\). Scale in milliseconds. Reference lines as before. Diamond \( A \)—fast input to compartments 1, 2, 9, and 10. Diamond \( B \)—fast input to compartments 1, 2, 3, 4, 9, and 10. Diamond \( C \)—fast input to compartment 3, 4, 9, and 10. Triangle \( A \)—medium input to compartment 1, 2, 9, and 10. Triangle \( B \)—medium input to compartments 1, 2, 3, 4, 9, and 10. Triangle \( C \)—medium input to compartments 3, 4, 9, and 10. Triangle \( E \)—weighted medium input into each of the 10 compartments. Arrows and solid symbols denote shift in EPSP shape indices obtained with a change in membrane time constant from 5 to 7 msec.

The EPSP shape denoted by \( E \) \((\text{triangle})\) results when synaptic input of medium duration is introduced into each compartment of the neuron model, with the intensities adjusted so that the resulting EPSP from each compartment, recorded at the soma, would have equal amplitude \((\text{cf. 4})\).

Thus, suitable combinations of proximal and distal inputs can produce EPSP shapes of the kind observed experimentally. The proximal input helps shorten the time-to-peak value while the distal input helps to lengthen the half-width duration. The longest half-width durations observed experimentally are still not successfully reproduced by these combinations of synaptic input locations, at least when using an assumed time constant of 5 msec. However, as discussed earlier, time constants of up to 7 msec are not uncommon in motoneurons. A change in the assumed membrane time constant simply involves a proportional shift of the computed shape index values away from the origin when plotted on a millisecond scale. Examples of such shifts are shown in Fig. 5 with arrows and small solid symbols, for a change...
in $\tau$ from 5 to 7 msec. Essentially all of the observed EPSP shape indices can thus be accounted for simply by varying synaptic locations and assumed membrane time constant, without postulating an additional variation in the time course of synaptic current.

The correspondence between observed miniature EPSP shapes and the shape of computed EPSP's does not prove that the experimental potentials arise in a system similar to the model. The model is sufficient but not necessary. However, the ability to mimic observed shape indices with relatively simple and apparently reasonable a priori assumptions is encouraging. The miniature EPSP's examined in this section were from the rhythmic sets examined in an earlier study (4). These undoubtedly involved a large number (unfortunately not determinable in most cases) of synaptic endings, and it seems reasonable that such a relatively large spray of endings might be distributed to the equivalent of several electrotonic compartments of the motoneuron studied. The results can in fact be explained on the basis of such a spatial distribution. Temporal dispersion in the occurrence times of inputs at the various end knobs may also be a factor governing the EPSP wave shape and less spatial dispersion is required in the model if one invokes a greater degree of temporal dispersion. It seems clear that the fastest observed miniature EPSP's can be accounted for quite well by more or less exclusively juxtasomatic input, while the remainder apparently require more distal dendritic inputs. Thus, the miniature EPSP's examined here can reasonably be thought of as arising from combinations of proximal and distal inputs in varying amounts, with the time course of distal inputs identical with, or perhaps only slightly slower than, the proximal inputs. It is conceivable that purely distal inputs may occur in nature, producing small EPSP's corresponding in shape to the theoretical restricted cases (Fig. 4, dashed line) but in such situations the potentials are probably too small to be recognizable with assurance and have not been studied as rhythmic EPSP's (cf. 5).

Dendritic electrotonic length

As stated in the introduction, the preceding calculations were made assuming a compartmental model with an electrotonic length equal to 1.8 times the characteristic length $\lambda$. As noted earlier (28), unpublished analysis of dendritic measurements provided by Aitken and Bridger (1) indicates that the electrotonic length of cat motoneuron dendritic trees corresponds to between one and two characteristic lengths. The actual radial extent of such a dendritic tree can be as little as half a millimeter away from the soma for small motoneurons, and as much as 2 mm for the largest cells. However, the largest dendritic trees have larger caliber dendritic trunks with large characteristic length constants; thus the electrotonic length may not differ greatly from that of smaller dendritic trees (19). Analyses of the voltage transients resulting from injection of constant-current pulses in motoneurons confirms the above-estimated range of dendritic electrotonic length (Rall and Nelson, unpublished observations and calculations). Nevertheless, it seemed
desirable to examine the effect of changes in dendritic electrotonic length on the shape indices of the computed EPSP's. Figure 6 illustrates the results of such an analysis. The dashed line represents the locus of computed EPSP shape indices shown in earlier figures and corresponds to a fast synaptic current time course and an electrotonic length of 1.8 λ for the nine dendritic compartments. The dashed-and-dotted curve represents the locus of shape indices assuming an electrotonic length of 0.9 λ for the nine dendritic compartments, while the solid line represents the shape index locus assuming an electrotonic length of 3.6 λ for the nine dendritic compartments. Clearly, increasing the electrotonic length of the model moves the points further away from the range of experimental observations (shaded area). Several attempts at combining proximal with distal inputs in the 3.6 λ model did not succeed in providing short enough time-to-peak values to fit the data points with longer half-width values. In the case of the 0.9 λ model, it is apparent that this cannot account for the longer half-width values. We conclude that the data are consistent with values for the dendritic electrotonic length (from soma to dendritic terminals) which lie in a range around 1.8 λ, but which does not extend down as far as 0.9 λ or up as far as 3.6 λ.

*Ratio of dendrites to soma.* The usual case of a chain of 10 equal compartments implies a surface area ratio of dendrites to soma of 9. Calculated EPSP’s have been produced utilizing a 5 equal-compartment model. This...
implies a surface area ratio of dendrites to soma of 4 and the results of these calculations are not markedly different from those presented in this paper (see 23 and 31 for anatomical estimates of dendritic and somatic surface areas). The ratio of steady-state dendritic input conductance to soma conductance has a value, \( p \), (25) which depends upon dendritic electrotonic length. Although the three cases illustrated in Fig. 6 all imply the same, dendritic to somatic surface area ratio, they imply rather different values for the ratio, \( p \), of steady-state dendritic input conductance to soma conductance (see 25). For the 0.9 \( \lambda \) case, \( p \) is about 7.2, for the 3.6 \( \lambda \) case \( p \) is about 2.5, and for the 1.8 \( \lambda \) case, \( p \) is about 4.8. This latter value can be regarded as a conservative estimate (25).

There is now substantial agreement between several lines of anatomical and physiological evidence indicating that the dendritic periphery is only 1 to 3 characteristic electrotonic lengths from the cell soma. Substantial potential changes can be expected, therefore, at the somatic trigger zone when synapses are activated in the periphery of the dendritic tree. The receptive area in the dendrites is large relative to that of the soma and most of the synaptic input to a neuron is thus dendritic. It is in the dendrites that much of the interaction between synaptic inputs may occur (see below). It is important to emphasize therefore that the entire dendritic tree must be considered in attempting to assess the functional significance of neuronal morphology.

**Electrically evoked EPSP's**

*Shape indices.* A plot of the shape indices for a number of evoked EPSP's has already been presented (Fig. 3, right). This region of the shape index plot can be filled with computed EPSP shapes generated in a variety of ways, including purely localized inputs, proximal-distal combinations, and certain kinds of uniformly distributed inputs. Because the miniature synaptic potentials are small, they can be summed with negligible nonlinearity (29). This means that for some purposes one can usefully look at the evoked EPSP as the summation of miniature synaptic potentials without attempting to discuss the location and time course of the many component synaptic currents responsible for its generation (4). Viewed from this perspective, the evoked EPSP, with its relatively prolonged falling phase, appears to include a significant proportion of miniature EPSP's of largely dendritic origin. Some temporal dispersion may be involved in the generation of the evoked EPSP but this probably is not sufficient to lengthen the falling phase to any great extent (cf. Fig. 4).

The generation of the evoked EPSP by synchronous activity in a number of group Ia fibers, therefore, appears to involve synaptic endings which are distributed over the entire receptive surface of the motoneuron, either uniformly (Figs. 4 and 5; solid line) or with some predominance in dendritic locations (cf. Fig. 5, E). The comparison of the computational model EPSP's with observed synaptic potentials, both miniature and evoked population responses, permits the general conclusion that spatial distribution of active
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input is apparently a sufficient condition in producing observed EPSP's. Any given experimental EPSP shape cannot be attributed to one unique combination of synaptic input time course and location; usually numerous combinations are possible. For example, the contribution of a slow input in compartment 1 can be very similar to that of a medium input in compartment 3, or that of a fast input in compartment 4. However, despite this kind of nonuniqueness, there can be little doubt that the entire range of observed EPSP shapes can be reproduced theoretically by using a model system and initial assumptions which appear to be reasonable approximations of the actual situation.

**Synaptic conductance and synaptic current.** It was not necessary to distinguish between synaptic current and synaptic conductance during the presentation of miniature EPSP shapes. In the actual computations, the synaptic current is caused by an excitatory conductance transient, but as long as the local membrane depolarization is small, the time course of the synaptic current differs negligibly from the time course of the conductance change. Thus, for the miniature EPSP computations, the synaptic input can be regarded either as synaptic current or as a synaptic conductance transient. However, as soon as larger depolarizations are considered, and nonlinearity in the summation of EPSP's and IPSP's is to be understood, it is necessary to specify the synaptic conductance transient and to realize that the amount and the time course of the resulting synaptic current depends also upon the effective driving potential which changes with membrane polarization.

**Generalizations about linearity of summation.** In our intuitive thinking about summations of EPSP's and IPSP's, we have occasionally made use of the following simplifying generalizations: nonlinear summation occurs when two inputs are at a common location, and linear summation occurs when two input locations are distant from each other. These oversimple generalizations arose from earlier theoretical explorations (28, esp. Fig. 9). While they have been helpful, these generalizations are not always reliable in this unmodified form; further computations (29) have helped to demonstrate the difficulties and permit a clarification of the problem. Thus, two inputs at the same location can add their effects with negligible nonlinearity as long as their separate effects are small enough; then the effective driving potential and hence the separate synaptic current contributions remain essentially unchanged. Also, two inputs at separate locations will add with significant nonlinearity provided that the membrane potential disturbance, caused by the input at one location, spreads to the other location in an amount sufficient to cause a significant change in the driving potential at the time of the synaptic conductance transient there; then the synaptic current generated at the second location is changed (reduced if both are EPSP's) by the presence of the input at the first location. The new generalization that emerges is that, while the distance between input locations is important, even more important is the percentage change in the effective driving potential, at the time and location
of one synaptic conductance transient, that is caused by the presence of the other synaptic input. When this percentage change is small, essentially linear summation occurs; when this percentage is large, a large amount of nonlinearity results.

**Observed nonlinearity.** When it is occasionally observed (e.g., ref. 4, Figs. 3 and 4) that two EPSP's of small amplitude (1–2 mv) sum with significant nonlinearity (say 10%), how can this be accounted for theoretically? This excludes placing both inputs at the soma, but the nonlinearity can easily be accounted for by placing both synaptic conductance transients at a common dendritic location, provided that the membrane depolarization produced at this location corresponds to about 10% of the driving potential, or about 7–10 mv. The location obviously must be dendritic to account for the difference between the small EPSP amplitude seen at the soma and larger amplitude needed at the synaptic input location. Even larger nonlinearity can be predicted for the case of larger local depolarization in a smaller (branching subdivision) or more peripheral dendritic location.

**PSP interaction.** The notion of wide spatial distribution of group Ia input to motoneurons is of importance in the interpretation of a variety of experimental observations, as will be discussed in PART II of this paper, and also enters significantly into attempts to understand the way in which neurons integrate synaptic information. The latter question has been dealt with in recent papers by Brookhart and his collaborators (3) and by Tersuolo and Llinas (33) (see also 25, 27, 28). The factor of spatial location of inputs enters into the process of temporal summation of synaptic potentials at a central summing point (the neuron soma) in that spatial factors control the duration of the PSP's at the soma (3). However, spatial location of inputs can also affect the resultant somatic PSP by mechanisms of local mutual interaction of the inputs at the generation sites, which may be distant from the cell soma (cf. 28). Indication of this has been presented in a previous paper (4) with regard to the summation of monosynaptic EPSP's; another example is shown in Fig. 7.

The data in Fig. 7 consist of averaged PSP records obtained in motoneurons with a CAT computer by techniques described earlier (4). Column A illustrates the linear summation of an EPSP generated by a lateral gastrocnemius nerve volley (upper trace in each set) with an IPSP from flexor digitorum longus stimulation (lower trace in each set) when the two PSP's were generated together (middle trace in each set) at different delays. The dots represent the algebraic summation of the top and bottom traces in each case. This type of interaction is in sharp contrast to the expected nonlinearity of summation illustrated by Curtis and Eccles (8, Figs. 5 and 6). The observations of Curtis and Eccles can be explained by assuming a dendritic EPSP and a somatic IPSP, with its effective driving potential increased by the somatically recordable EPSP. Linear interaction (Fig. 7A), however, implies that there is very little mutual interaction at the generator sites of the two potentials, and this appears to necessitate that both were produced on den-
dritic sites at some distance from the soma and at some distance from each other. The opposite extreme is seen in column B, with data obtained from another gastrocnemius motoneuron. In this case, interaction between a lateral gastrocnemius EPSP and an extensor digitorum longus IPSP led to markedly nonlinear summation, much more than would have been expected merely on the basis of proportional displacement of the IPSP driving potential (cf. 8). This situation again suggests that the generator sites of both PSP’s were at some distance from the soma, but were close enough to one another to permit considerable mutual interaction to take place. In a series of over 40 such EPSP-IPSP interactions studied, most of the examples showed intermediate degrees of nonlinearity, consistent with Curtis and Eccles’ data (8), but the few cases at either end of this spectrum illustrate the range of observations possible. No meaningful pattern in terms of reflex behavior was evident in this series of interactions; the importance for discussion here is the demonstration that spatial distribution of synaptic input over the extended receptive membrane of a neuron can explain a wide variety of experimental observations.

PART II: ASSESSMENT OF POSSIBLE EPSP MECHANISMS

Preceding papers in this series and PART I of the present paper have emphasized that, in spinal motoneurons, many of the synapses mediating the monosynaptic EPSP are distributed on the distal dendrites. This dendritic location (and in particular the dendritic core resistance between the synaptic location and the soma) serves to determine many of the properties of the EPSP as recorded in the motoneuron soma. This makes the specification of the membrane mechanism underlying these dendritically generated EPSP’s
difficult. For purpose of the present discussion concerning the membrane mechanisms of the EPSP we will focus our analysis upon those synapses which may be assumed to be at or near the recording site in the soma.

Much of the literature on possible synaptic mechanism is concerned with a dichotomy between "chemical" and "electrical" models of synaptic transmission (see 11 for review). We shall begin with a brief description of these two types of model and discuss the possibilities of distinguishing between them. Figure 8 represents a generalized model of the synaptic region and includes both electrical and chemical models, depending on the relative values which are assigned to the circuit components.

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**Fig. 8.** Generalized sketch and equivalent circuit of synaptic region at cell soma. Lettered points on sketch correspond to similarly designated points in the circuit. $Z_A =$ resting presynaptic fiber input resistance. $R_s =$ presynaptic resistance during the presynaptic action potential. $Z_1 =$ presynaptic membrane resistance between the inside of the presynaptic fiber and the synaptic cleft. $Z_2 =$ subsynaptic postsynaptic membrane resistance; this remains fixed in the case of the electric model of synaptic transmission, but would fall during chemical synaptic transmission. $R_N$ and $C_N =$ lumped resistance and capacitance approximating the electrical characteristics of the postsynaptic neuron. $R_L =$ lateral access or "leak" resistance from the synaptic cleft to the extracellular fluid. Membrane potential batteries are omitted except for that representing the presynaptic spike which is in series with $R_s$.

*Chemical synapse or postsynaptic ionic permeability transient.* This designates the general class of synaptic mechanisms in which an ionic permeability transient is triggered in the postsynaptic membrane by presynaptic activity (13). Although the trigger is most commonly assumed to be a chemical transmitter substance, the general class of mechanisms includes the possibility of other kinds of triggers, such as mechanical or electrical. In Fig. 8 the permeability transient would be represented by a transient decrease in the value of $Z_2$ (the impedance of the subsynaptic membrane of the postsynaptic cell). This model implies that the lateral access resistance or "leak" resistance to the extracellular volume from the synaptic cleft ($R_L$, Fig. 8) is relatively low as discussed in detail by Eccles and Jaeger (12).

*Electric coupling synapse.* This term is used to designate the general class of synaptic mechanisms in which the presynaptic action potential (represented by closing $Sw$ in Fig. 8) is the driving force for the EPSP, and the
postsynaptic membrane portion of the synapse (Z\textsubscript{2} in Fig. 8) does not undergo a transient change in its properties. For this mechanism to be effective Z\textsubscript{2} acts as passive coupling between the two cells. A requirement of this class of mechanism is that R\textsubscript{L} must be very large (see below). The properties of this electrically coupled synapse depend strongly upon the relative values of the resting presynaptic fiber resistance (Z\textsubscript{A}) and the coupling resistance (Z\textsubscript{1}+Z\textsubscript{2}).

Low resistance electric coupling. When the over-all coupling or contact resistance (Z\textsubscript{1}+Z\textsubscript{2}) between the presynaptic and postsynaptic cytoplasm is low enough relative to the resting input resistance of the presynaptic terminal, such a synapse will appear to undergo a transient of postsynaptic membrane conductance, even though it actually does not. This can be seen intuitively from Fig. 8. If R\textsubscript{s} (presynaptic resistance during the spike) is much less than Z\textsubscript{A}, the closing of Sw here replaces the high resistance of Z\textsubscript{A} (resting presynaptic fiber resistance) with the low resistance of R\textsubscript{s} and this “un-masks” the low, constant coupling resistance (Z\textsubscript{1}+Z\textsubscript{2}). Under resting conditions, the low coupling resistance is masked because it lies in series with the large resting resistance Z\textsubscript{A} of the presynaptic element. The presynaptic impulse thus results in an apparent transient of postsynaptic membrane conductance. Because of this similarity between the “chemical” synapse and the low resistance electric coupling synapse, in later discussions the term “conductance transient” will refer to either of these mechanisms.

High resistance electric coupling. If the over-all coupling resistance (Z\textsubscript{1}+Z\textsubscript{2} in Fig. 8) is high with respect to Z\textsubscript{A}, the change in presynaptic resistance during the presynaptic action potential has a negligible effect on the apparent postsynaptic membrane resistance. This case thus resembles a high impedance current source or a “constant current” source.

The “high” and “low” resistance electric coupling models represent the extreme cases in which (Z\textsubscript{1}+Z\textsubscript{2}) is either much higher or much lower than Z\textsubscript{A} in Fig. 8. Intermediate relationships between (Z\textsubscript{1}+Z\textsubscript{2}) and Z\textsubscript{A} would result in synaptic properties intermediate between those described above.

We wish to summarize evidence with regard to the monosynaptic EPSP in spinal motoneurons which is relevant to the problem of discriminating between the categories listed above as possible mechanisms for the EPSP. Three kinds of observations are incompatible with the high-resistance electric synapse (high impedance or constant current) as a mechanism for the EPSP.

1) In about one-half of the monosynaptic EPSP’s examined, an impedance change could be demonstrated during the EPSP (32). While the time course of the impedance change was not usually that predicted by the simplest conductance transient model, a change in cell impedance very early in the course of the EPSP was seen in some of the EPSP’s. This is incompatible with the high resistance electric coupling model of the synapse, so the EPSP’s which were accompanied by an impedance change must have been due to a conductance transient mechanism. In addition, the synapse
generating these EPSP’s must have been close to the soma in order for the impedance change to be detectable (29, 32). Independent evidence for the location of the synapses generating a given EPSP is provided by the shape indices discussed earlier in this paper. When the shape indices of the EPSP’s in the impedance study were analyzed, a correlation between synaptic location and impedance change was evident. The shape indices of the EPSP’s showing an impedance change were indicative of a proximal location of the synapses generating those EPSP’s. Conversely, the EPSP’s without an associated impedance change appeared to be generated by more distally located synapses. This result is shown in Fig. 9. Those EPSP’s with detectable impedance changes (●) are located in the lower, left-hand part of the graph—the area corresponding to EPSP shapes obtained with proximally located synapses; whereas those without impedance changes (○) group toward the upper, right-hand part of the graph—the area corresponding to the EPSP shapes obtained with distally located synapses. The straight line and dotted outline correspond to those presented in previous figures of this paper. It is clear from the over-all correspondence of the data that the two studies were dealing with samples of EPSP’s with similar shape indices.

2) While a majority of EPSP’s summate in a linear fashion, a significant minority do not (4). Within the limits seen experimentally, there is no clear correlation between the size of the EPSP’s and the linearity of their summation. Nonlinearity of summation can be explained on the basis of the conductance transient model, whereas the high resistance electric coupling synaptic model would predict linear summation of all EPSP’s.

3) Many EPSP’s exhibit an increased rate of rise when the postsynaptic membrane is hyperpolarized (7, 24). This indicates an increased synaptic current which may or may not be associated with an increased EPSP amplitude. The increased synaptic current with hyperpolarization of the postsynaptic membrane is not compatible with the high resistance electric...
DENDRITIC SYNAPSES AND EPSP MECHANISMS

The failure of the EPSP to increase in amplitude despite an increased synaptic current may be explained on the basis of anomalous rectification in the motoneuron (24).1

In a small sample of cells, those EPSP's which did not show an increased synaptic current with membrane hyperpolarization appeared to be generated in the distal dendrites, as indicated by their shape indices. The spectrum of effects on the EPSP produced by polarizing currents is thus compatible with a conductance transient model, and with the notion of widely distributed synaptic locations (24).

The conclusion from the foregoing evidence is that the monosynaptic EPSP in motoneurons cannot be generated by the high resistance electric coupling type of synapse. As pointed out earlier, these results do not distinguish between the low resistance electric coupling synaptic model and a chemical, postsynaptic permeability transient model.

We have considered various other sorts of evidence which might be relevant to the mechanism of EPSP generation. These include the latency for the EPSP or synaptic delay, the effect on the EPSP of high stimulus repetition rates, the interaction between the motoneuron spike and the EPSP and posttetanic potentiation of the EPSP. None of these lines of evidence appear to us to provide a decisive indication as to the basic nature of EPSP mechanism and therefore do not warrant further discussion here.

There are certain kinds of evidence which can, in principle, allow a distinction between the electrical and chemical models. With regard to chemical transmission, an important body of evidence is the in vivo demonstration of the presumed chemical transmitter substance and of its liberation during activity of the presynaptic axons, of the transmitter's ability to produce the requisite PSP and associated conductance change, and of an in situ means of transmitter removal. While such experiments are simple in concept, they are extremely difficult in execution, and in cat motoneurons attempts to demonstrate an EPSP transmitter have been unsuccessful (9). For electrical transmission, a crucial result would be the ability to pass current from the presynaptic to the postsynaptic element more easily than from the extracellular region to the postsynaptic element. Such experiments have been performed successfully in fish (2) but there have been no reports of such experiments in mammals. Demonstration of such electrical coupling would imply a very high cleft access resistance (RL in Fig. 8) and, as has been noted, this is a necessary assumption of the electrical model. Such a high cleft access resistance implies cleft dimensions approaching those of the "tight junction" that have been observed in a number of preparations. While such tight junctions have been seen in the amphibian and fish spinal

1 Although a few computations were carried out with reduced membrane resistance, the theoretical model in its present form does not provide for anomalous rectification. Another complication not provided for is the observation that EPSP's decay usually ends in an after-hyperpolarization (7); we believe, however, that the time to peak and the half-width of the observed EPSP's are not significantly affected by this delayed complication.
cord, they have not been seen in the mammalian spinal cord (6). Theoretical calculation (12), based on the anatomical cleft dimensions usually seen in the mammalian central nervous system, give low estimates of synaptic cleft access resistance. Thus the presently available anatomical evidence does weigh in favor of the chemical model for mammalian motoneurons, but because of uncertainties in the anatomical methods (see 16) such evidence is not conclusive.

When changes in the ionic composition of the postsynaptic cytoplasm produce changes in PSP characteristics, this has been thought to be strong evidence for the chemical or postsynaptic model. The recent findings, however, that certain ions (Bennett, personal communication) and even large molecules (21) can traverse some electrical intercellular junctions mean that postsynaptically injected ions could affect either electrically or chemically mediated synaptic potentials. The reported lack of PSP alteration by injected ions may represent an "ion-tight" electrical synapse or a distally located synapse of either the chemical or electrical type. The difficulty in demonstrating an effect on a (presumably) chemical distal synapse by somatically injected ions has been shown by Terzuolo and Llinas (33). Thus, the report that after changing the ionic composition of the motoneuron cytoplasm "... the EPSP was not significantly altered" (7) leads to no clear conclusion. If, however, changes in the somatic ionic composition produce no alteration in selected EPSP's with shape indices pointing to a largely somatic location of the synaptic input, this would be strong evidence against the chemical model.

One line of evidence that would discriminate between the chemical and electrical models has to do with the effects on the EPSP of large depolarizing current. If an EPSP can be completely and unequivocally reversed in sign by such current, this is strong evidence for the postsynaptic chemical model. On the other hand, if an EPSP has shape indices suggesting a proximal site of generation and if the EPSP does not reverse when the membrane potential is forced beyond the EPSP's presumed equilibrium potential, this is strong evidence against the chemical model. Complete EPSP reversal has been reported (7). In our hands, the form of the EPSP reversal was complex and the decreased signal-to-noise ratio which is obtained when large currents are passed through the microelectrode raised some doubts as to the total reversal of the earliest phases of the EPSP. Furthermore, in a sample of eight cells, there was no correlation between the presence or absence of apparent reversibility of the EPSP's and the shape indices of the EPSP's. Both the rarity and the complex nature of the EPSP reversal suggest that occult disynaptic EPSP's or IPSP's may have been present in those few PSP's which have been apparently reversed. In view of these doubts, we are reluctant to place crucial reliance on the data presently available.

In summary, we have discussed the evidence bearing on the question of the membrane mechanisms involved in the generation of monosynaptic EPSP's in motoneurons. A number of lines of evidence serve to exclude the
high coupling resistance electrical model of synaptic transmission. In view of the uncertainties which attach to the crucial lines of evidence, we feel that an unequivocal decision between the chemical and the low coupling resistance electrical models is unwarranted at this time.

SUMMARY

1. The predictions of a mathematical neuron model have been compared with observations on monosynaptic EPSP's recorded from cat spinal motoneurons.

2. Quantitative comparisons between computed and observed EPSP shapes have made use of "shape index plots": EPSP shapes are represented as points in a plot of half-width versus time-to-peak.

3. The fastest observed EPSP shapes can be theoretically accounted for by synaptic input restricted to the neuron soma; the slowest observed EPSP shapes can be theoretically accounted for by a dendritic distribution of synaptic input. Intermediate shapes can be accounted for by various combinations of proximal and distal dendritic synaptic input locations. Most of the observed EPSP shapes differ significantly from those predicted theoretically for uniform synaptic input over the entire soma-dendritic receptive surface.

4. Additional support for this theoretical interpretation of the observed EPSP shape variety is provided by observations made with polarizing currents and impedance bridge techniques. The slower EPSP shapes correlate with small effects of polarizing current and with failure to detect impedance transients, as would be expected for a predominantly distal dendritic input location. In contrast, the faster EPSP shapes correlate with large effects of polarizing current and with success in detecting an impedance transient, as would be expected for predominantly somatic and proximal dendritic synaptic input.

5. The notion of wide spatial distribution of group Ia synaptic input on the motoneuron receptive surface adequately explains the experimentally observed range in the linearity or nonlinearity of postsynaptic potential interactions.

6. On the basis of our computations and physiological observations, we conclude that the synapses of group Ia afferent fibers are widely distributed over the motoneuron surface and that even those synapses located on the distal dendrites can produce significant depolarizations at the soma.

7. Several models of synaptic mechanisms, both chemical and electrical, have been discussed and assessed for adequacy in accounting for the monosynaptic EPSP in spinal motoneurons. For distal dendritic input locations, the various synaptic mechanisms are essentially indistinguishable. For somatic and proximal dendritic input locations, various experimental observations imply a conductance transient that rules out the high coupling resistance electric model. However, both a mechanism involving a postsynaptic permeability change (chemical transmission model), and a mechan-
ism involving low-resistance electric coupling (electrical transmission model), are consistent with most of the presently available evidence.

REFERENCES