A MATHEMATICAL MODEL FOR SPREADING CORTICAL DEPRESSION

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ABSTRACT A mathematical model is derived from physiological considerations for slow potential waves (called spreading depression) in cortical neuronal structures. The variables taken into account are the intra- and extracellular concentrations of Na^+, Cl^-, K^+, and Ca^{++}, together with excitatory and inhibitory transmitter substances. The general model includes conductance changes for these various ions, which may occur at nonsynaptic and synaptic membrane together with active transport mechanisms (pumps). A detailed consideration of only the conductance changes due to transmitter release leads to a system of nonlinear diffusion equations coupled with a system of ordinary differential equations. We obtain numerical solutions of a set of simplified model equations involving only K^+ and Ca^{++} concentrations. The solutions agree qualitatively with experimentally obtained time-courses of these two ionic concentrations during spreading depression. The numerical solutions exhibit the observed phenomena of solitary waves and annihilation of colliding waves.

INTRODUCTION

Spreading depression (SD) was discovered by Leão (1944) in the course of his experimental studies of epilepsy. SD is a slowly traveling wave phenomenon, since elicited in a variety of brain structures in a variety of animals. Its speed is amazingly independent of the structure, usual values being between 2 and 6 mm/min. Observations indicate that an SD wave propagates only through regions of gray matter composed chiefly of cell bodies, dendritic processes, unmyelinated axons, and glial cells.

The first observation of SD was through one of its concomitant effects, namely depression of the normal electroencephalographic pattern of activity. If the DC surface potential of the brain structure relative to some reference electrode (e.g., on temporal muscle) is measured during SD, the most noticeable feature is a sustained negative wave with amplitude between 5 and 15 mV lasting from 1 to 2 min. (If the geometry of the neurons is reversed, as in the olfactory bulb, then the wave is positive.) Some SD waves are preceded by, and sometimes followed by, a surface positive wave usually of smaller amplitude than the main negative component. SD waves are also

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observable below the surface, where the amplitude depends on the depth of the recording electrode in the cortical structure. In rat cerebral cortex a fascinating set of experiments by Shibata and Bureš (1972, 1974, 1975) has demonstrated the persistence of SD waves by reverberation around closed loop pathways. An extremely comprehensive review of SD, its concomitant biochemical effects, experimental methods for its elicitation, and early theoretical considerations has been compiled by Bureš et al. (1974).

During the passage of SD through a neuronal structure, the individual neurons and glia show characteristic behavior. Neurons invariably cease their spiking activity for most of the duration of the wave. Usually they increase their rate of spiking at the onset of the wave and also during the recovery period. Sometimes the initial bursting is followed by a short silence, then a short burst, and then the characteristic longer silence. The membrane potentials of individual neurons and glia have been measured during SD (Higashida et al., 1974; Sugaya et al., 1975) and typically show a sustained depolarization whose rising phase is more abrupt than its return to its usual value. The time-course of the depolarization of single cells corresponds roughly with that of the surface wave.

More recently, external ion concentrations have been measured during SD. Kraig and Nicholson (1976) reported a large increase in the concentration of K^+ and large decreases in the concentrations of Na^+ and Cl^-. Nicholson et al. (1977) measured the time-courses of the external concentrations of K^+ and Ca^{++} during SD. The K^+ concentration increased and declined in approximate correspondence with the neuronal and glial depolarizations, whereas Ca^{++} showed the opposite behavior. These two ions play a central role in the model to be presented here.

It is interesting that SD waves, which occur in populations of neurons, have many wave properties (Bureš et al., 1974) in common with those action potentials that occur in the axons of single neurons. Amongst these we find that both: (*a*) are approximately all-or-none phenomena; (*b*) travel with approximately constant speed and wave form; (*c*) involve depolarization of neuronal membrane; (*d*) exhibit refractoriness and relative refractoriness; (*e*) have multiple waves generated from a strong sustained stimulus; (*f*) show annilhilation of colliding waves.

Although SD and action potentials both depend on ionic fluxes through neuronal membrane, important qualitative and quantitative differences must be accounted for in the development of a mathematical model for SD: (*a*) space and time scales are longer for SD than for action potentials; (*b*) SD propagation seems to depend mainly on ionic fluxes through synaptic membrane with some contributions from nonsynaptic membrane (see below for supporting evidence), whereas action potentials propagate by means of fluxes through nonsynaptic membrane; (*c*) SD waves propagate with substantial changes in extracellular ion concentrations (Kraig and Nicholson, 1976), whereas during passage of an action potential the ion concentrations change by negligible amounts; (*d*) active transport mechanisms are probably essential for the recovery phase of SD but are not significant in the repolarization phase of action potentials.

SD can be instigated by a variety of means. The stimuli that may be used include:

(*a*) chemical, e.g., application of KCl, glutamate, and more recently ACTH (Jakobartl and Huston, 1977); (*b*) mechanical, e.g., by impact or wounding; (*c*) electrical; (*d*) physiological, i.e., intense neuronal stimulation; and (*e*) ultrasound (Ueda et al., 1977). The propagating SD wave shows an amazing independence of its method of instigation.

Perhaps the most curious thing about SD is the question of its functional significance. Many physiologists consider it a pathological phenomenon and a nuisance when it arises accidentally in the course of an experiment. Physiological psychologists have been interested in its effects on learning and behavior as SD forms a transient reversible functional ablation of the tissue through which it passes. Recently it has been suggested that SD might play a role in normal behavior (Jakobartl and Huston, 1977). It has been implicated in concussion (Bureš, 1959) and migraine accompanied by scotoma (Lashley, quoted in Bureš, 1959). SD has often been studied in the retina, where its effects may be observed visually (Gouras, 1958).

Our objective in this paper is to derive a model for SD based on available physiological information. The experimental results used to generate the model come from many studies on diverse structures and we will have to extrapolate information from these studies to develop the mathematical model. The parameters of the model have definite physiological definitions, but due to lack of detailed information on any particular structure, we will in this first study assume values for these parameters that give rise to solutions with the correct qualitative behavior.

MECHANISMS INVOLVED IN SD

A mathematical model for the conduction of impulses in cardiac muscle due to Wiener and Rosenblueth (1946) was quoted as being relevant to SD (Shibata and Bureš, 1972), but we feel it is not appropriate in this context. A computer simulation approach was pursued by Reshodko and Bureš (1975), but the physiological mechanisms were not incorporated in the model nor quantified to any extent.

Since K^+ is an important ion in determining neuronal and glial membrane potentials and because its extracellular concentration has been shown to follow approximately the time-course of depolarization of neurons and glia during SD, it is not surprising that this ion is a necessary component of the model to be developed. Potassium was the ion whose behavior was modeled in a previous theoretical investigation (Grafstein, 1963). If $u(x, t)$ is the concentration of K^+ in the extracellular space at time t, then, as suggested by Hodgkin (unpublished communicated to Grafstein [1963]), the governing equation was postulated to be

$$u_t = Du_{xx} + f(u), \tag{1}$$

where f is a cubic of the form $u(u - u_1)(u_2 - u)$ with u_1 and u_2 both positive constants, D is the diffusion coefficient, and x is distance measured in the direction of propagation of the SD wave. The only stable, steady-progressing wave solutions of this equation are saturating ones (Fife, 1977) and so the only part of the SD cycle taken

into account was the elevation of external K^+. Expressions for such solutions were found by Huxley (see Graftstein, 1963). One may obtain an *ad hoc* complete with repolarization if one adds a "recovery" term in Eq. 1 to give

$$u_t = Du_{xx} + f(u) - \epsilon \int_0^t u(x, t')\, dt', \quad \epsilon > 0, \tag{2}$$

the FitzHugh-Nagumo equation (FitzHugh, 1961; Nagumo et al., 1962), sometimes used to mimic the behavior of the Hodgkin-Huxley system of equations (Hodgkin and Huxley, 1952).

Grafstein argued that potassium released by neuronal spiking was the instigator of SD (which is undoubtedly true in some cases) and that the spiking in neighboring neurons induced by diffusion of K^+ enabled the wave to spread. From recent experiments, however, it is known that SD can propagate through cortical structures treated with tetrodotoxin (TTX) (Sugaya et al., 1975). This chemical blocks the fast sodium conductance changes necessary for action potentials, so neuronal spiking cannot play an essential role in SD.

The fact that SD propagated in TTX-treated cortex without any spiking implies that synaptic mechanisms not triggered by action potentials are important in SD. For example, increased extracellular K^+ around a rat neuromuscular junction produces separate rapid (~minutes) and slow (~half an hour) effects on the transmitter release system (Gage and Quastel, 1965). In further support of this idea is the blocking of SD by Mg^{++} (Shibata and Bureš, 1975), known to block synaptic transmission in many preparations by antagonizing the inward Ca^{++} currents needed for transmitter release (Katz, 1969; Krnjevic, 1974). It is known that TTX does not interfere with postsynaptic conductance changes induced by the suspected neurotransmitter L-glutamate (Zieglgänsberger and Puil, 1972), nor does it interfere with nonsynaptic K^+ conductance. Thus synaptic conductance changes will still be operative in TTX-treated cortex along with certain TTX-insensitive conductance changes on nonsynaptic membrane. Large concentrations of $CaCl_2$ (119 mM/liter threshold [Shibata and Bureš, 1975]) also block SD. A possible explanation is that this is a "chloride block" (Leão, 1972). The rapid effect of increased extracellular K^+ on the transmitter release system mentioned above has been shown to be blocked by a high Ca^{++} concentration (Cooke and Quastel, 1973). Another possibility is that additional Ca^{++} substitutes for Ca^{++} on postsynaptic receptors (Krnjevic, 1974, in the case of L-glutamate; Neumann and Chang, 1976, in the case of acetylcholine) so that released transmitter, which operates by removing Ca^{++} bound to receptors, is rendered ineffective. Other explanations for the block of SD by divalent cations are clearly possible, and for quantitative relations and further discussion see Bureš et al. (1974).

Another finding implicating synaptic mechanisms in SD propagation is that apical dendrites seem to play an important role (Ochs, 1962). These processes have a high density of (usually excitatory) synapses. Thus, instead of K^+ released by neuronal spiking, it seems that K^+ released from postsynaptic cells due to depolarization of synapses plays an important role in the spread of the SD wave.

There is a controversy as to the primary chemical involved in SD propagation. Van Harreveld (1959) postulated that the putative neurotransmitter glutamate might be the primary agent in SD propagation in the rabbit cortex. This idea was further discussed with reference to SD in chicken retina (Van Harreveld and Fifková, 1970; Fifková and Van Harreveld, 1974). The view that glutamate rather than potassium ions plays a central role has not been generally accepted (Do Carmo and Leão, 1972; Bureš et al., 1974). In reality many chemicals are involved in SD and it is difficult to single out one as central. In the model set forth here K^+ will be the primary agent, in the sense that its diffusion to neighboring cells will be the trigger for the chain of events that lead to the release of more K^+ and other ions. There will occur with the wave of K^+ an almost simultaneous wave of transmitter substances, so that in some sense our theory unifies the two previous physical theories, if glutamate is the relevant transmitter substance. Mathematical models may be used to resolve this controversy. It should be pointed out, however, that Grafstein (1956) applied electric fields to isolated cat cortical slab and found that the velocity of SD propagation was increased (decreased) when the field was applied so that positive ions would be accelerated (decelerated) in the direction of propagation. She therefore hypothesized that "the spread of response is determined by the movement of K^+."

Another consideration in modeling SD is the possible role of glial cells. There are believed to be as many as 10 glial cells to every neuron in vertebrate nervous systems (Kuffler, 1967), though they are much smaller than most neurons and probably occupy only about half the volume of the brain. These cells are distinct from neurons in many ways. They do not have action potentials, they may divide, and one of their functions is to dispose of damaged neurons. They are thought to be mediators of nutrient supply to neurons, as they have direct contact with blood capillaries. Physiologically glia act chiefly as K-electrodes (Kuffler, 1967; Ransom and Goldring, 1973). They also have uptake and release mechanisms for various amino acids (Minchin and Iversen, 1974; Roberts and Keen, 1974) and ions (Gill et al., 1974; Latzkovits et al., 1974). It has been found, however, that diffusion of chemicals is preferentially around glial cells through the intercellular clefts. It was reported that their intracellular concentration of K^+ does not change significantly when the extracellular concentration of this ion is increased (Nicholls and Kuffler, 1964). Müller cells in frog retina during SD undergo an increase in internal K^+ concentration (Mori et al., 1976), indicating that the observed increase in external K^+ is due to release from neurons rather than glia. The idea has been advanced that glia play an important role in SD (Higashida et al., 1974), but we will not treat glial cells in the main part of the model because it seems they are fairly passive in SD. Since the model will predict the time-course of external K^+, the glial membrane potential can be easily obtained via the Nernst formula.

DERIVATION OF THE MODEL EQUATIONS

The anatomical system we consider is typical gray matter with its high density of cell bodies and dendrites with their synaptic coverings. We will, to simplify and to enable us to study the basic phenomenon of interest, treat only one spatial dimension and as-

sume that the structure is spatially homogeneous. The treatment in two or three space dimensions is complicated by the need to consider anisotropic diffusion of ions and the geometrical nonhomogeneities. Because the diameters of most of the nerve cell processes and synaptic boutons are on the order of a few microns (though apical dendrites may extend for hundreds of microns) and the relevant length scale for SD is millimeters, we will treat the various chemicals in the model as varying continuously in space as well as time. We will speak of extracellular and intracellular concentrations at the same point, though in reality these quantities will be defined over discrete intervals. In other words, on the length scale appropriate for a study of SD, we can neglect the discontinuities at neuronal boundaries. If we cite an intracellular concentration, say, at point x, then this will mean, in terms of the actual neuronal structure, the concentration at the nearest set of intracellular points. It is emphasized, however, that mechanisms at the individual cell level are taken into account.

The rate of change of the neuronal membrane potential, apart from the transient spiking initially and during the repolarization phase, is so slow in SD that the capacitive current essential to action potential generation is negligible. If action potentials are taken into account during SD, then additional sources and sinks for the various ions would have to be included. The relevant time scale for SD is seconds, long compared to the usual time scale (milliseconds) for action potentials.

Fig. 1 shows an idealized picture of the subsystem whose physiological components we shall focus on in developing a model for SD. A presynaptic terminal is shown with membrane potential V_2. The terminal contains neurotransmitter (possibly in vesicular form) that may be excitatory or inhibitory with respect to the postsynaptic membrane. The extracellular space is indicated and normally contains the ions Na^+, Cl^-, and

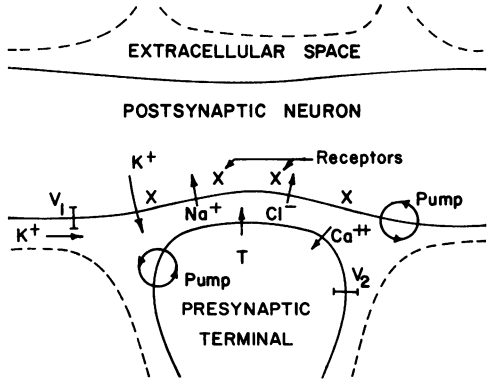

FIGURE 1 Schematic representation of the anatomical and physiological details of the microsystem on which the model for SD is based. Potassium ions are shown diffusing in from the left, ahead of the SD wave front. The post- and presynaptic membrane potentials are denoted V_1 and V_2. Ions are shown where their normal concentrations are higher; T denotes transmitter substance. The associated arrows represent directions of flow during the rising phase of the SD wave. Pumps are shown in both pre- and postsynaptic membrane. Receptors are denoted by crosses and the dashed lines represent either neighboring neuronal processes or glial cells.

Ca^{++} in high concentrations relative to their intracellular concentrations. The intracellular compartments usually have a high concentration of K^+ relative to the extracellular concentration of this ion. A part of a postsynaptic cell is shown with membrane potential V_1. The receptors on the subsynaptic membrane are the sites at which conductance changes for the various ions occur when transmitter substance is released from the presynaptic terminal. The rate of transmitter release is believed to be related to the calcium current into the terminal, though aspects of transmitter release are still under experimental investigation. There will also be a calcium flux into the postsynaptic cell but this is not explicitly taken into account here. Hence calcium currents are only taken into account insofar as they effect transmitter release. Active transport mechanisms (pumps) are shown located in both pre- and postsynaptic membranes, their main function being to restore the normal distributions of the ions. Pumps are also often invoked as mechanisms for the uptake of certain amounts of transmitter substances into the presynaptic terminals, but these pumps will not be included in our model.

The concentrations of the various ions at the spatial point x and at time t will be denoted by $C_j^o(x, t)$ in the extracellular space and by $C_j^i(x, t)$ in the intracellular compartments. The subscript j will take the values 1, 2 3, and 4 for sodium, chloride, potassium, and calcium, respectively (order of increasing atomic weight). The concentrations of excitatory and inhibitory transmitter substances in the extracellular space (in particular in the synaptic clefts) will be designated $T_1(x, t)$ and $T_2(x, t)$, respectively. The intracellular (presynaptic) concentrations of these substances will not be taken into account because transmitter in presynaptic terminals produce conductance changes only after release into the cleft.

Since we are only concerned with equilibrium membrane potentials, we assume that the membrane potentials for neighboring pre- and postsynaptic membranes do not differ significantly and hence take for their common value $V_1 = V_2 = V(x, t)$. This is justified during SD because the large ratio of the intracellular to extracellular volumes results in small changes in the intracellular concentrations of the ions (K^+, Na^+, and Cl^-), which determine the equilibrium membrane potential. That is, changes in V are determined chiefly by the extracellular concentrations of these ions.

The value of this membrane potential will be assumed to be given by the Goldman-Hodgkin-Katz formula (see, e.g., Plonsey [1969])

$$V = (RT/F) \ln [(C_3^o + p_1 C_1^o + p_2 C_2^i)/(C_3^i + p_1 C_1^i + p_2 C_2^o)], \tag{3}$$

where R is the universal gas constant, T is the absolute temperature, and F is Faraday's constant. The quantities p_1 and p_2 are the ratios of the sodium and chloride permeabilities of the membrane to the potassium permeability. The effects of other ions on V is neglected. With each ion there is associated a Nernst equilibrium potential

$$V_j = (RT/z_j F) \ln (C_j^o/C_j^i), \quad j = 1, 2, 3, 4, \tag{4}$$

where z_j is the valence. The glial cell membrane potential is thus approximately given by the potassium Nernst potential, V_3.

In the extracellular space, ions are free to diffuse from one part of the cortical structure to another, whereas intracellular ions can only diffuse within a limited region of space or must first become extracellular before becoming free to diffuse over significant distances. The model equations are thus diffusion equations with sources and sinks for the extracellular ions and first-order differential equations for the intracellular ions. Hence the intracellular ion concentrations increase or decrease according to fluxes from or into the extracellular space.

The basic evolution equations for the ion concentrations are thus

$$\frac{\partial C_j^o}{\partial t} = D_j \frac{\partial^2 C_j^o}{\partial x^2} + g_j(V - V_j) + P_j, \tag{5}$$

$$\frac{\partial C_j^i}{\partial t} = -\frac{\alpha}{1 - \alpha}[g_j(V - V_j) + P_j], \tag{6}$$

where $j = 1, 2, 3, 4$ and D_j is the diffusion coefficient for the j^{th} ion species. The meaning of each of the last two terms in Eq. 5 is as follows. We assume there is a membrane "conductance," g_j, and an associated driving potential, which is the difference between the membrane potential and the Nernst potential for the jth ion. Thus the currents $g_j(V - V_j)$ will, properly scaled, be the contribution of the "passive" membrane fluxes to the rate of change of the ion concentrations in the extracellular space. The terms P_j represent the contribution of active transport mechanisms (pumps) to the ionic fluxes and will be positive or negative depending on the direction of transport. Since conservation of the total number of ions is assumed, any ions that leave the extracellular compartment alter the intracellular concentration. Hence, the rate of change of the latter is given by Eq. 6, which is just the negative of Eq. 5 without the diffusion term and with the scale factor $\alpha/(1 - \alpha)$, α being the fraction of the structure that is extracellular space. Note that α may have different values depending on whether the intracellular compartment referred to is pre- or postsynaptic. This complication will be neglected in the following.

Contributions to the g_j will come from nonsynaptic and subsynaptic membrane. We now need to distinguish sodium, chloride, and potassium from calcium, which plays a special role. For the former group of ions we assume that nonsynaptic membrane is relatively unimportant in SD. There is some evidence (though certainly not conclusive) that this kind of membrane conductance has an appreciable effect over relatively small fractions of the total neuronal surface, for the main part densely packed with synaptic endings (see, e.g., Conradi, 1969; Rinvik and Grofova, 1970; Dodge and Cooley, 1973). It is not possible at present to estimate the effect of neglecting nonsynaptic membrane conductances. We will proceed to focus on contributions to the g_j that result from transmitter release, as the model so obtained predicts the correct qualitative behaviors of the ion concentrations during SD.

The calcium conductance of the presynaptic membrane, expected to play a relevant role, is assumed to be a function of the presynaptic membrane potential only, so that $g_4 = g_4(V)$. The dependence on V is expected to show a threshold-type behavior, as

found for squid stellate ganglion cells by Llinás et al. (1976). From these experimental data, we assume that the transmitter release rate is proportional to the presynaptic calcium current,

$$\partial T_i/\partial t \propto g_4(V)(V - V_4), \quad i = 1,2. \tag{7}$$

A more complete equation for the rate of change of transmitter concentration could be written down with diffusion and active transport terms, but since transmitter may play only a transient role at a given location, we do not pursue this complication here. This transient role manifests itself in the concept of effective transmitter substance at time t. The total amount of transmitter of type i released up to time t is obviously proportional to

$$\int_0^t \frac{\partial T_i}{\partial t'} \mathrm{d}t'. \tag{8}$$

If the transmitter substance is only effective for a brief time, τ, (on the order of milliseconds), then the effective amount of transmitter at time t is

$$T_i^*(x,t) \propto \int_{t-\tau}^{t} g_4(V(x,t'))[V(x,t') - V_4(x,t')]\,\mathrm{d}t'. \tag{9}$$

We now assume that at time t the conductance of the subsynaptic membrane for the j^{th} ion species ($j = 1,2,3$) induced by transmitter of type i is proportional to the effective amounts of transmitter i present:

$$g_j(x,t) = \sum_{i=1}^{2} k_{ij} T_i^*(x,t), \quad j = 1,2,3, \tag{10}$$

where the k_{ij} are constants.

In summary, the general model equations for the system are given by

$$\left.\begin{aligned} \frac{\partial C_j^o}{\partial t} &= D_j \frac{\partial^2 C_j^o}{\partial x^2} + \left(\sum_{i=1}^{2} k_{ij} T_i^*\right)(V - V_j) + P_j, \qquad (11)\\ \frac{\partial C_j^i}{\partial t} &= -\frac{\alpha}{1-\alpha}\left[\left(\sum_{i=1}^{2} k_{ij} T_i^*\right)(V - V_j) + P_j\right], \qquad (12) \end{aligned}\right\} j = 1,2,3,$$

$$\partial C_4^o/\partial t = D_4 \frac{\partial^2 C_4^o}{\partial x^2} + k_4 g_4(V - V_4) + P_4, \tag{13}$$

$$\partial C_4^i/\partial t = -\frac{\alpha}{1-\alpha}[k_4 g_4(V - V_4) + P_4], \tag{14}$$

where k_4 is a lumped physiological parameter containing the amount of presynaptic membrane per unit distance in the direction of propagation of the SD. These equations form a system of four reaction-diffusion equations for the extracellular ion concentrations, coupled with a system of four ordinary differential equations for the intra-

cellular ion concentrations. Together they form a complicated system, despite our very simplified approach.

A SIMPLIFIED MODEL INCLUDING ONLY K^+ AND Ca^{++}

The ions K^+ and Ca^{++} play special roles in the general model. Potassium concentrations have the greatest effect on the membrane potentials and calcium is presumed instrumental in the release of transmitter substances that produce postsynaptic conductance changes leading to ion fluxes. It seems, and is borne out by the numerical results, that a model that neglects the fluxes of Na^+ and Cl^- should exhibit the basic SD phenomena. We have pursued this simplified model to reduce considerably the large amount of computing time needed to solve the complicated system of Eqs. 11–14. In the simplified model it is convenient to change the notation: K^o and K^i denote external and internal K^+ concentrations, C^o and C^i denote Ca^{++} concentrations, and subscripts K and Ca will be used in place of 3 and 4.

We adopt two further simplifications: (*a*) the synaptic conductance changes for K^+ due to excitatory and inhibitory transmitter can be lumped into a single term; and (*b*) the time τ for which transmitter remains effective is so small that we make the following approximation,

$$\int_{t-\tau}^{t} g_{Ca}(V)(V - V_{Ca})dt' \simeq \tau g_{Ca}(V)(V - V_{Ca}), \tag{15}$$

where V and V_{Ca} on the right side are evaluated at time t. Furthermore, the results of Llinás et al. (1976) lead us to assume that the dependence of calcium conductance on depolarization can be approximated by the sigmoidal function

$$g_{Ca}(V) = g_0(1 + \tanh [p_g(V + V_g)]), \tag{16}$$

where g_0, p_g, and V_g are constants.

The membrane potential, given by Eq. 3, depends on the concentrations of Na^+ and Cl^-, but in the simplified model these are held fixed. The effect on V of neglecting sodium ion fluxes is not expected to be great because of the small relative permeability of Na^+. However, the chloride contribution to V is more significant. The flux of this ion into the neurons during the depolarization phase of SD could be due to its accompaniment of sodium ions to partially maintain electroneutrality (Van Harreveld and Fifková, 1973) or due to activation of inhibitory synapses. Neglect of this flux means a reduced depolarization as seen from Eq. 3. Furthermore, the diffusion of chloride and sodium near the wave front will be in a direction opposite to the propagation of the SD wave. The local decrease in external chloride produces a more rapid depolarization (noting that $p_2 \gg p_1$) and hence will probably contribute to a decrease in the speed of the wave.

In the real neuronal structure the rates at which ions are actively transported across the various membranes are determined not only by the ion concentrations but also by the stimulation of metabolic processes that involve the release of energy by cleavage

of ATP. The associated metabolic turnover during SD has been studied by fluorescence techniques (Rosenthal and Somjen, 1973; Mayevsky and Chance, 1974). The observed increase in metabolism corresponds roughly with the repolarization phase of SD (although it is difficult for a precise correspondence to be established) and has been shown to be a consequence of, rather than an instigator of, SD. To avoid the introduction of additional variables to describe the details of these metabolic processes, we will assume that the pump rate for each ion depends only on the difference between the concentration of that ion and its resting value. In the model the direction of transport will determine whether the intracellular or extracellular concentration of the ion should be used and the pump terms will always restore that concentration to its resting level. In reality there will be complications such as overshoot, the exchange nature of certain pumps, and inhibition of pump rates by the presence of large quantities of another ion. These complications will not be taken into account here.

Studies of the pump rates for a given ion have revealed a saturating effect at large concentrations, indicating a maximum number of available pump sites in a given membrane area (Sjodin and Ortiz, 1975; Sachs, 1977). For a pump that returns extracellular ions to the intracellular compartment, as is the case for K^+, a suitable expression for the pump consistent with an assumed zero pump rate at resting concentration and saturating at large external concentrations is

$$P_K = -f_K(1 - \exp[-r_K(K^0 - K_R^0)]), \tag{17}$$

where f_K and r_K are positive constants and K_R^0 is the resting value of external K^+ concentration. It is realized that the pump rate is not in fact zero in the resting state because the resting membrane potential is maintained only with a small pump rate to handle the leakage of K^+ out of the cell. Here, however, we are concerned with departures from the resting conditions. The negative sign in Eq. 17 indicates that the pump decreases the extracellular concentration of K^+. The expression may be derived from probabilistic arguments by consideration of ion collisions with pump sites.

It might seem strange that our K^+ pump term depends only on extracellular K^+ when it is generally thought that Na^+ and K^+ are actively transported on an exchange basis. There is also evidence that activation of the Na^+–K^+ pump in cat cortex depends in part on the level of intracellular Na^+ (Heinemann and Lux, 1977). It is known, however, that the K^+ transport rate does not depend entirely on the presence of intracellular Na^+ for frog sartorius muscle fibers (Sjodin and Ortiz, 1975). In fact, the potassium influx rate is 10 μmol/g h for zero internal Na^+ concentration for this preparation. Our justification for Eq. 17 is that the changes in internal Na^+ (actually neglected in our simplified model) will be about the same as the changes in external K^+ (based on Kraig and Nicholson, 1976).

With the above simplifications and assumptions, the complete simplified model equations become, at 37°C,

$$V = 58 \log_{10}[(K^0 + \gamma)/(K^i + \delta)], \tag{18}$$

$$V_K = 58 \log_{10}[K^0/K^i], \tag{19}$$

$$V_{Ca} = 29 \log_{10}[C^0/C^i], \tag{20}$$

$$K_t^0 = D_K K_{xx}^0 + \rho_1 g_{Ca}(V)(V - V_{Ca})(V - V_K) + P_K, \tag{21}$$

$$K_t^i = -[\alpha/(1 - \alpha)][\rho_1 g_{Ca}(V)(V - V_{Ca})(V - V_K) + P_K], \tag{22}$$

$$C_t^0 = D_{Ca} C_{xx}^0 + \rho_2 g_{Ca}(V)(V - V_{Ca}) + P_{Ca}, \tag{23}$$

$$C_t^i = -[\alpha/(1 - \alpha)][\rho_2 g_{Ca}(V)(V - V_{Ca}) + P_{Ca}], \tag{24}$$

$$P_K = f_K(1 - \exp[-r_K(K^0 - K_R^0)]) + f_K^*, \tag{25}$$

$$P_{Ca} = f_{Ca}(1 - \exp[-r_{Ca}(C^i - C_R^i)]) + f_{Ca}^*, \tag{26}$$

where subscripts t and x's denote partial derivatives, γ and δ contain the (assumed) constant concentrations of Na^+ and Cl^-, previously introduced constants are collected in ρ_1 and ρ_2, and f_K^* and f_{Ca}^* in the pump terms are necessary because our choice of g_{Ca} means there will be some leakage of K^+ and Ca^{++} at resting levels.

NUMERICAL RESULTS

To test the simplified model, we numerically computed the solutions to the initial-value problems leading to the traveling wave solutions and to the annihilation of two waves upon collision. The equations were finite-differenced in space and a Runge-Kutta scheme was used to march forward in time. Because of the size of the time step used and the operation of the Runge-Kutta package, it was necessary to set the source terms, namely the passive current terms and the pump terms, equal to zero when $V <$ 70 mV, $K^0 < 2$ mM/liter, and $C^i < 0.05$ mM/liter to prevent the extracellular potassium and intracellular calcium ion concentrations from going negative. This is no restriction since these source terms normally prevent the extracellular potassium and intracellular calcium concentrations from going below their resting levels. One further complication in the model, which apparently does not lead to any difficulties when coupled with this cutoff, is that the system of Eq. 18–26 themselves do not have a unique rest state. However, except for the diffusion term, there is conservation of the ion number between the intracellular and extracellular spaces and, as will be seen from the numerical results, the ion concentrations return to the initial resting levels.

Though we had hoped to obtain physiological estimates of all the parameters in Eqs. 18–26, this has not been possible due to lack of data on any particular neuronal structure. We will pursue this approach and report the results at a later date. Some heuristic understanding of the behavior of the solutions was obtained by several trial runs, considering the necessary values of the parameters that would make the various source and sink terms in the equations give rise to the approximate values of the rates of change of the experimentally observed ion concentrations. In the results given and discussed below, the following parameter values and initial values were used. Some of these are approximately based on actual values from diverse studies on various structures (see the Appendix): $D_K = 2.5 \times 10^{-5}$ cm^2/s, $D_{Ca} = 1.25 \times 10^{-5}$ cm^2/s, $g_0 = 0.015$ mho/cm^2, $p_g = 0.11$ (mV)$^{-1}$, $V_g = 45$ mV, $\alpha = 0.2$, $\rho_1 = -5$ mM cm^2/liter/s/

mho/mV^2, ρ_2 = 0.5 mM cm^2/liter/s/mho/mV^2, γ = 9 mM/liter, δ = 40 mM/liter, f_K = −5.2 mM/liter/s, f_{Ca} = 0.052 mM/liter per s, r_K = 10 liter/mM, r_{Ca} = 40 liter/mM, K_R^o = 2.0 mM/liter, C_R^i = $C^i(x,0)$ = 0.05 mM/liter, $K^i(x,0)$ = 140 mM/liter, $C^o(x,0)$ = 1.0 mM/liter. The values of f_K^* and f_{Ca}^* are then determined by setting them equal and opposite to the values of the net source and sink terms evaluated at resting levels. Because of the imposed cutoffs, f_K^* = f_{Ca}^* = 0 for the results below. In light of our ignorance of accurate values of the parameters, the only possible comparison with experiment, at present, is a qualitative one.

Solitary SD Wave

A local Gaussian distribution of K^+, representing an application of excess K^+ in the form of say, KCl, was added to the resting extracellular level to give a peak value of 40 mM/liter. Due to the spatial symmetry of the initial ion concentrations and the equations, this gives rise to two SD waves, one moving to the left, the other moving to the right. Fig. 2 follows the one moving to the right and shows the concentrations of extracellular K^+ and Ca^{++} as functions of distance at various times. The initial distributions of extracellular K^+ and Ca^{++} are shown at t = 0 and the resulting waves at

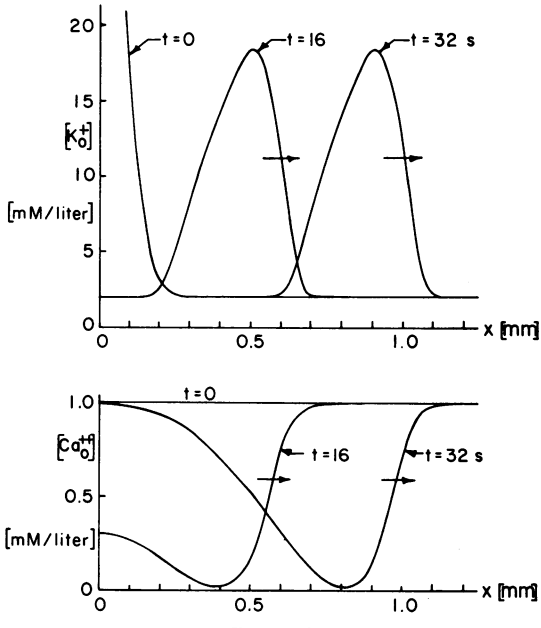

FIGURE 2

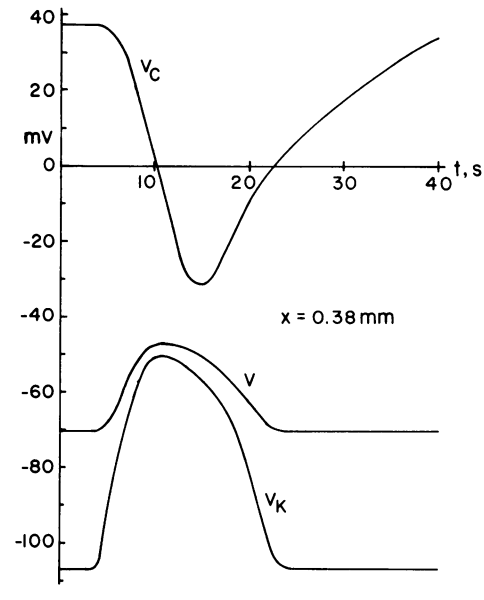

FIGURE 3

FIGURE 2 Solitary SD waves in response to a local excess of K^+ centered at x = 0. Solutions of the simplified model equations for external potassium and calcium concentrations as a function of distance in the direction of propagation. The initial distributions are shown at t = 0 and the resulting waves of increased K^+ and decreased Ca^{++} are shown for t = 16 and 32 s.

FIGURE 3 The time-course of the membrane potential V and the potassium and calcium Nernst potentials during passage of the solitary SD wave at the point x = 0.38 mm. Note that V_K and hence V return to their resting values well ahead of V_{Ca}.

times t = 16 and 32 s. The solutions seem to be steady, progressing waves of increased K^+ and decreased Ca^{++} with monophasic profiles. The front of the wave exhibits the characteristic rapid increase in the K^+ concentration and slightly less rapid decline in the Ca^{++} concentration. It is noted that K^+ returns to its resting level before Ca^{++} returns to its initial values. This feature is consistent with the experimental results for these ions (Nicholson et al., 1977). In our model, if Ca^{++} returned to its initial values before K^+ returned to its resting level, there is the possibility of a second wave being generated.

The propagation velocity of the waves shown in Fig. 2 is about 1.5 mm/min. A slower speed is obtained if allowance is made for the circuitous path of ions around neurons and glia in the intercellular clefts. If cell processes are assumed to be cylindrical obstacles (clearly an oversimplification), then a scale factor of about $\pi/2$ should be applied to distances in the model. (See the Appendix for more discussion on geometrical factors and effective diffusion coefficients.) Hence the velocity of the SD wave corresponding to the numerical solutions of the model equations in an actual structure would be about 1 mm/min. This is slightly below the experimental range of velocities of SD (2–6 mm/min; Ochs, 1962). Several factors could increase the wave speed. The rate of increase in the extracellular potassium concentration is less than observed experimentally (Nicholson et al., 1977); therefore, the source terms in the model could be increased, which would result in an increased speed. Contributions to the increase in the extracellular $[K^+]$ from fluxes through nonsynaptic membrane (e.g., during action potentials), neglected here, would clearly increase the wave speed. In fact, the results obtained with the model we have investigated and experimental results should only be compared with reference to TTX-treated cortex. We should emphasize that even in this case, an exact comparison of the wave speeds from the model and experiments is premature because we have not as yet been able to obtain accurate parameter values for the various source and sink terms. Similar remarks apply to the durations (for fixed x) of the membrane potential and extracellular K^+ waves computed from the model and observed in TTX-treated cortex (see Fig. 14 in Sugaya et al., 1975), which are shorter than observed in normal cortex.

Fig. 3 shows the time-courses at a fixed spatial point of the membrane potential and the potassium and calcium Nernst potentials as the SD wave passes by. As SD enters the region, K^+ increases abruptly, decreasing (in magnitude) both the potassium Nernst potential, V_K, and the membrane potential, V. External Ca^{++} decreases less rapidly and this is reflected in the slower decline of V_{Ca}. The potassium efflux becomes exceedingly small when the potassium Nernst potential and the membrane potential are almost equal. This means a reduction in passive K^+ efflux so the pump can then dominate, causing the return of extracellular K^+ to its initial value. When V is about equal to V_K, the difference between V and V_{Ca} is still quite large, so the force driving Ca^{++} into cells is not yet negligible, and dominates the calcium pump. However, the value of V_{Ca} eventually becomes quite close to V, making the Ca^{++} influx very small, so that now the calcium pump is dominant and calcium ions are returned to the extracellular space. Meanwhile, excess K^+ has diffused forward around relatively nonde-

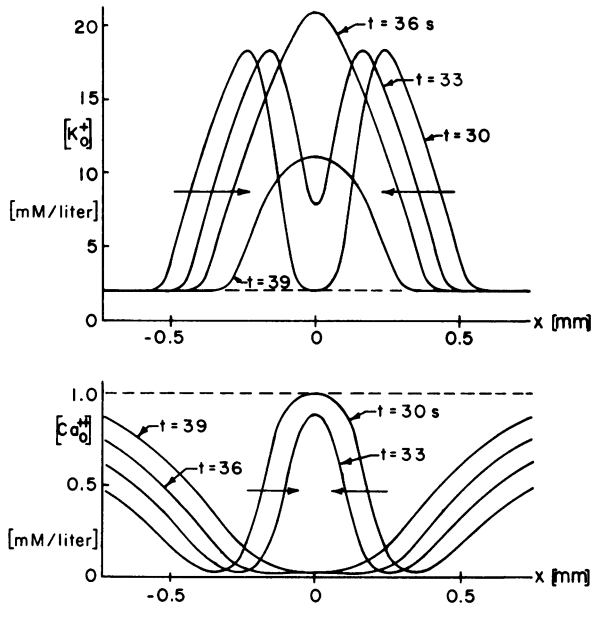

FIGURE 4 Annihilation of SD waves. Two solitary waves are generated at the ends of an interval and approach each other. The potassium and calcium ion concentrations are shown just before the collision at $t = 30$ s. At $t = 33$ s the two waves have partially collided. The distinction between the two waves is lost at $t = 36$ s. Finally the potassium wave decays towards the resting level at $t = 39$ s. Note that the calcium ion concentration has not yet begun to return to its resting level at $x = 0$.

polarized regions to start the same chain of events. When conductance changes for K^+ and Ca^{++} occur, these ions move so as to make their concentrations equal inside and outside the cells. The subsequent repolarization is a natural property of the system that has not yet been analyzed. It is noteworthy that the repolarization occurs without conductance inactivation or transmitter depletion (both of which cannot be excluded from consideration).

Annihilation of Colliding SD Waves

SD waves that meet each other head on are known to annihilate each other. We ran two solitary SD wave solutions into each other in our model cortical structure and the results, shown in Fig. 4, clearly demonstrate the phenomenon of annihilation. Again K^+ must return to its initial concentrations before Ca^{++} returns to its initial values to prevent the start of new waves.

CONCLUSIONS

The simplified model system thus successfully predicts the basic qualitative properties of SD waves in real neuronal structures. Knowledge of the physiological parameters of the model is incomplete but we feel that this model is a starting point for future quantitative work. It is feasible that other models that focus on different mechanisms, in par-

ticular for the repolarization phase of SD, would also successfully predict the properties of SD waves. We have focused solely on transmitter release and its subsequent postsynaptic conductance changes as the source of K^+. A complete model would have to take into account contributions from nonsynaptic membrane, but we have elected to ignore this complication. Much further theoretical and experimental work is needed before a complete understanding of the fascinating phenomenon of SD can be obtained.

Finally, we point out that reverberating SD waves could be studied within the framework of the above model by including a second space dimension. The introduction of a vertical dimension is probably necessary to explain the characteristic DC slow potential changes measured at the surface and the observed distribution of potential as a function of depth in the cortex. These additional features will be considered in later papers.

APPENDIX

Parameter Values in the Numerical Calculations

As pointed out in the main text, it was not possible to obtain accurate values of the parameters in the model Eqs. 11–14 and in the simplified model Eqs. 18–26 for which numerical solutions are reported. To illustrate the difficulties, the parameter ρ_1 in Eq. 21 involves: (*a*) the time for which transmitter is effective in producing conductance changes in postsynaptic membrane; (*b*) the conductance change produced in postsynaptic membrane per unit area per unit quantity of released transmitter; (*c*) the calcium ion conductance of presynaptic membrane per unit area at large depolarizations; (*d*) the areas of post- and presynaptic membrane in a column of cortex of unit length in the direction of propagation of the SD wave. (Further complications arise if one considers the depth dimension—both (*b*) and (*d*) will vary throughout the various cortical layers.) Since all of these physiological and anatomical variables are not known for any specific cortical structure (nor even any one of them as far as we know!), we adopted a heuristic and partly phenomenological approach to estimate many of these parameters for use in the simplified model equations.

The resting value of external K^+ concentration, 2 mM/liter, was taken from Kraig and Nicholson's (1976) results for the molecular layer of the cerebellum of *Corydoras aneus*. The resting value of external Ca^{++} concentration, 1 mM/liter, is based on Nicholson et al.'s values of 1.0 mM/liter for cat 0.7 mM/liter for rat cerebellum (1976, 1977, respectively). The resting internal K^+ concentration, 140 mM/liter, is approximately the value given for cat spinal motoneurons (Eccles, 1957), and was chosen in conjunction with the constants γ and δ, which contain contributions from Na^+ and Cl^- concentrations and the permeabilities of these ions, to give a resting membrane potential of about -70 mV. This is close to the average potential of -67 mV reported for 14 stable cells in rabbit cerebral cortex (Collewijn and Van Harreveld, 1966). The resting internal Ca^{++} concentration, 0.05 mM/liter, was chosen to be of the same order of magnitude as the estimate of 0.01 mM/liter for the concentration of unbound Ca^{++} in squid axon (Hodgkin and Keynes, 1957).

The parameter α, the fraction of cortical tissue that is extracellular (intercellular) space was set at 0.2, the average of the values of 0.05 and 0.35 given by Blinkov and Glezer (1968). The value 0.2 was also given by Lux and Neher (1973) for cat cortex.

The values of the diffusion coefficients, $D_K = 2.5 \times 10^{-5}$ cm^2/s and $D_{Ca} = 1.25 \times 10^{-5}$ cm^2/s, are based on the values for aqueous diffusion given in the American Institute of Physics Hand-

book (1963). Assuming that the diffusion coefficients of K^+ and Ca^{++} in the extracellular fluid of the brain are about those in aqueous solutions means that x, the spatial coordinate, measures the path length of ions around the various neuronal and glial processes. This can be converted to distance traveled by the SD wave by allowing for geometric factors. Though we suggest a factor of $\pi/2$ to allow for cylindrical obstacles, we realize that the true situation is much more complicated. McLennan (1957), for example, suggested a scale factor of 2 be applied to the diffusion coefficients to allow for slowing by various obstructions. When diffusion occurs through narrow clefts, a scaled diffusion coefficient is sometimes appropriate (Nicholls and Kuffler, 1964) but these authors deduced that for small ions such as K^+ this scaling was not necessary. Lux and Neher (1973) suggested an effective diffusion coefficient $D_K^* = D_K/6$ in cat cortex but this scaling involved both geometric considerations and unquantifiable cell source and sink mechanisms. Similarly, Fisher et al. (1976) have found that the effective diffusion coefficient for K^+ in the "vertical" direction of cat cortex is about 2.86×10^{-6} cm^2/s, but claimed that the low value of the diffusion coefficient relative to its value in aqueous solution was due to the "tortuosity of the extracellular space" and other "unknown factors."

The parameters p_g and V_g in Eq. 16, which determine the variation (but not the magnitude) of the calcium conductance of presynaptic membrane with depolarization were obtained as follows. From the data of Llinás et al. (1976) on the squid giant synapse, the shape of the variation of $g_{CA}(V)$ with V was obtained by assuming a value of $V_{Ca} = 150$ mV (based roughly on data for squid axon [Hodgkin and Keynes, 1957]) and then dividing the measured presynaptic (peak) calcium current by $(V - V_{Ca})$; this gives $p_g = 0.11$. The value of V_g was set at 45 mV to make the abrupt increase in presynaptic calcium conductance occur at the value of V expected during the initial rising phase of the K^+ concentration, as measured by Nicholson et al. (1977) for rat cerebellum, allowing for our choice of γ and δ and the resting external and internal K^+ concentrations.

The remaining parameters are g_0, ρ_1, ρ_2, which determine the magnitudes of the source term for K^+ and the sink term for Ca^{++}, and the four pump parameters f_K, r_K, f_{Ca}, and r_{Ca}. The experimentally measured time-courses of K^+ and Ca^{++} guided us in our choice of values for these parameters (Nicholson et al., 1977). At typical external K^+ and Ca^{++} concentrations in the early part of the depolarization phase of SD, the various terms in Eqs. 21–24 were computed. The strength of the source term for K^+ (determined by the product of g_0 and ρ_1) was chosen to dominate the K^+ pump term, while simultaneously the sink term for Ca^{++} (involving $g_0\rho_2$) dominated the Ca^{++} pump term. The values were chosen in such a way to ensure that the computed $\partial K/\partial t$ and $\partial C/\partial t$ values in the model equations were about the same as the corresponding experimental values. Typical values of the ion concentrations at the peak of the SD wave were then considered and the strengths of the sources and sinks in the model computed. Here it had to be ensured that the K^+ pump term dominated the K^+ source term and the Ca^{++} pump term dominated the Ca^{++} sink term. Again an approximate match of the $\partial K/\partial t$ and $\partial C/\partial t$ values predicted by the model and the experimental values of these rates of change during the repolarizing phase of SD was sought. After examination of the effects of various combinations of parameters, the values given in the text were found to give the desired solitary wave solutions with approximately the correct order of magnitudes for the rates of change of the external ion concentrations.

This work would not have been complete without the obtaining of numerical solutions of the model equations. That task was admirably performed with great perseverance by Richard C. Lee. We have been guided by and consulted with numerous people in the course of this work: Doctors D. M. J. Quastel, E. Puil, T. Hattori, E. McGeer, J. H. Quastel, H. McLennan, J. J. Miller, and S. Assaf of the University of British Columbia; Drs. H. Higashida and J. Rinzel of the National Institutes of Health, Bethesda, Maryland; Dr. E. Goldensohn of Columbia University, New York; Dr. A. Van Harreveld of the California Institute of Tech-

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