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On the Production and Release of Chemical Transmitters and Related Topics in Cellular Control

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This paper makes some neurophysiological and biochemical predictions concerning transmitter production and release which are suggested by psychological postulates. A main theme is the joint control of presynaptic excitatory transmitter production by presynaptic and postsynaptic levels of membrane potential. This control is presumed to be effected by the interaction of the pairs (Na^+, K^+) and (Ca^{++}, Mg^{++}) of antagonistic ions whose binding properties to intracellular sites and enzymes set various cellular production levels. It is suggested that nerve cells are capable of learning as 'chemical dipoles'. A qualitative rationale is discussed for such phenomena as the following: joint inward fluxes of Na^+ and Ca^{++} due to membrane excitation; distribution of mitochondria and synaptic vesicles near the synaptic cleft; sensitivity of RNA interaction to Mg^{++} concentration; stronger binding of Ca^{++} relative to K^+ within the synaptic knobs; mobilization and depletion of transmitter by presynaptic spiking; post-tetanic potentiation; excitatory transients in transmitter release after a rest period; feedback inhibition of transmitter onto a late stage of transmitter production; transport down the axon of some lighter molecules produced in the cell body; proportionality of cell body membrane area to nuclear volume; intracellular tubules as faithful transport mechanisms between nerve cell body and nucleus, and from nucleus along axon to synaptic knobs; division of cell shape into a cell body, axon, and synaptic knobs as a structural manifestation of the underlying chemical dipole.

1. Introduction

The first stages of a learning theory with psychological, physiological, and biochemical implications were derived in Grossberg (1969*a*,*b*). The note by Grossberg (1968) summarizes some of the main ideas of these papers, and also lists some results of the present paper. Since the theory is derived on a psychological basis, its mathematical variables from the start have psycho-

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logical labels, such as "presentation of a letter or spatial pattern at time t_1", "guess of a letter at time t_2", "stimulus trace", "associational strength", etc. Given this psychological theory, one then notices that its mathematical variables are already in a form that suggests a neurophysiological, anatomical, and in some cases biochemical labeling of these variables. Naturally the leap from psychological (or macroscopic) to neural (or microscopic) variables cannot be deductively justified, if only because psychological phenomena are averages, in a suitable sense, over individual neural events. This leap ultimately depends on qualitative arguments and general rules of prudence. Fortunately the simplest neural labeling often seems to yield functional relationships (via the psychologically derived laws) which represent, at least qualitatively, known and nontrivial neural data, or even in some cases new predictions.

This paper aims at deriving information concerning some of the more rapidly varying and spatially localized neural interactions—which are not always clearly visible in the psychological model—by slowing down the time scale and chopping fine the spatial variables of the psychological equations. Some of the qualitative conclusions arrived at in this way are listed below.

(a) Learning needs suggest that the level of excitatory transmitter production is controlled jointly by presynaptic and postsynaptic levels of membrane excitation.†

(b) This joint control is perhaps effected by an interaction of the two pairs (Na^+, K^+) and (Ca^{++}, Mg^{++}) of antagonistic ions, such that

(c) a predominantly presynaptic source of Na^+—supplied by the action potential—and a predominantly postsynaptic source of Ca^{++} serve as synergistic cofactors in activating within the synaptic knob those sites, or enzymes, which control the final stages of excitatory transmitter production, say of acetylcholine.

(d) Thus, an inward movement of Na^+ and Ca^{++} during membrane excitation is expected, and

(e) to avoid the destruction of cellular 'memories' immediately upon a return to membrane equilibrium, Ca^{++} and/or Na^+ are more likely to be found in bound form within the synaptic knob than is K^+.

(f) These ionic movements are compatible with some data concerning the pattern of ion translocation in the mitochondrion, and with the assumption (say) that these ionic movements free adenosine 5'-triphosphate in order to facilitate production of acetyl-Co A, and thereupon acetylcholine, under the guidance of choline acetylase in the synaptic vesicles; see, for example, Fruton and Simmonds (1958).

† The referee has kindly informed the author of the related work of J. S. Griffith (*Nature, Lond.* **211,** 5054, 1160) and A. M. Uttley (1966) (*Brain Res.* **2,** 27). It is perhaps also proper to mention the author's unpublished Dartmouth Senior Fellowship papers of 1959–61 which culminated in a monograph and a series of papers distributed in 1964–65 from The Rockefeller Institute.

(g) The suggested need of both pre- and post-synaptic ionic sources for mitochondrial regulation of graded amounts of transmitter production in the synaptic knobs makes plausible the intra-endbulb distribution of mitochondria and synaptic vesicles near the synaptic cleft.

(h) The existence of an Mg^{++} (or possibly an Na^+–Mg^{++}) activated system in the postsynaptic cell body which is not found in the synaptic knobs is suggested by two factors: (i) the postulated release during postsynaptic excitation of Ca^{++} for possible binding within presynaptic endbulbs, and (ii) the antagonism between Ca^{++} and Mg^{++} as cofactors. The postsynaptic nerve cell nucleus is an obvious structure that might contain this system.

(i) It is natural to hope that the Mg^{++} (or Na^+–Mg^{++}) activated nuclear system regulates certain cellular production levels, since the Na^+–Ca^{++} activated endbulb system serves a similar purpose. The sensitivity of nuclear RNA activation to Mg^{++} concentration and the central role of the RNA's in guiding protein synthesis are qualitatively compatible with this expectation.

(j) Thus systematic RNA changes during learning experiments can be contemplated without assuming that behavioral memories are stored in individual RNA strands. The present theory suggests, by contrast, that these memories are spread over large collections of cells and that the response of individual cells aims merely at keeping themselves metabolically tuned to such varying environmental demands as fluctuating excitatory and inhibitory inputs.

(k) The endproducts of nuclear activation by Mg^{++} cannot be manufactured with equal ease in the synaptic knobs without destroying the Ca^{++} bias therein. These endproducts are nonetheless needed, presumably for maintenance throughout the cell. Hence a flow of these endproducts from cell body along the axon to the synaptic knobs is called for.

The above items describe a kind of chemical dipole inside nerve cells whose more rapidly varying interactions are controlled by a hierarchy of ionic binding strengths among pairs of antagonistic ions. Some structural properties of nerves can plausibly be discussed as manifestations of this hypothetical dipole. For example:

(l) The above learning needs suggest a cell nucleus which is localized in the cell body rather than being spread throughout the nerve, and an interpretation of cell body and synaptic knobs as the structural endpoints of the underlying chemical dipole.

(m) Structures are needed within the cell interior to guarantee faithful transport of regulatory chemicals between the cell body membrane and nucleus, and from the nucleus along the axon to the synaptic knobs. A system of intracellular tubules, such as in endoplasmic reticulum, is a plausible candidate for these tasks.

(n) Production within the cell body of the correct amounts of certain regulatory chemicals needed by the entire cell suggest an idealization of a nerve cell (say without dendrites) in which cell body membrane area is proportional to nuclear volume and to the total membrane area of axon and synaptic knobs. This idealization is a special case of the property of spatio-temporal self-similarity, which is also manifested in the proportionality between axon diameter and spike velocity along the axon.

(o) Because of the self-similarity property, the size of this idealized cell can, in principle, be controlled by a single gene whose activity is sensitive to the average total membrane excitation.

An underlying theme in the above discussion is that learning needs make plausible some of the highly inhomogeneous features of nerve cell structure. In particular, the chemical dipole postulated within the cell's interior would severely distort the transfer of environmental signals along the cell if these were not rapidly carried by the action potential along the outer cell membrane.

We also find the following transient effects in our equations:

(p) Presynaptic spiking both mobilizes and depletes excitatory transmitter. Whereas the steady-state mobilized transmitter that is released per unit time increases as a function of steady-state spiking frequency, and saturates at a finite value, the total steady-state mobilized transmitter decreases as a function of spiking frequency.

(q) A slowly varying form of post-tetanic potentiation occurs in the synaptic knobs.

(r) An excitatory transient in transmitter release occurs when presynaptic spiking is resumed after a rest interval.

(s) The amount of intracellular transmitter is regulated in part by a feedback inhibition within the synaptic knob of the transmitter acting on a previous stage of transmitter production. This inhibition must affect an intermediate or terminal stage of transmitter production, or else behavioral memories would be destroyed.

(t) Transmitter release from synaptic knobs is coupled to intracellular K^+ concentration.

Grossberg (1968) describes some other conclusions, both psychological and physiological, derived from the theory, and states related references.

All of the above conclusions are limited in their quantitative accuracy by the fact that they are derived at a level of the theory for which individual spikes are invisible and only spiking frequencies are described. The passage from spiking frequencies to individual spikes will naturally yield nontrivial conceptual improvements of the formalism, such as a discussion of some influences of transient membrane currents on the axonal firing threshold.

Many of the above qualitative conclusions have been found experimentally. The theory tries to provide a unifying conceptual framework through which sometimes seemingly unrelated or unintuitive data can be plausibly discussed as manifestations of a few underlying principles that lie close to our macroscopic intuitions. To expose this framework, the remainder of the paper contains a rather detailed and discursive description that might profitably be preceded by reference to Grossberg (1968).

2. A Brief Review

The process depicted in Fig. 1 is derived from psychological postulates in Grossberg (1969*a*,*b*).

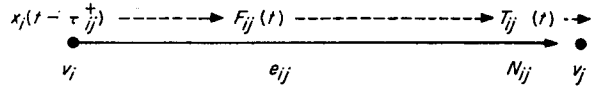

FIG. 1

In every time interval $(t-\tau_{ij}^+,\ t-\tau_{ij}^+ + dt)$, the cluster of cell bodies v_i with average membrane potential $x_i(t-\tau_{ij}^+)$ gives rise to an average spiking frequency

$$F_{ij}(t) = \beta_i^+[x_i(t-\tau_{ij}^+)-\Gamma_{ij}^+]^+ p_{ij}^+, \tag{1}$$

at the left-hand endpoint (or axon hillock) of the axons e_{ij}^+. The notation $[w]^+$ in (1) denotes

$$[w]^+ = \max(w, 0).$$

Γ_{ij}^+ is the average spiking threshold of the axons e_{ij}^+, p_{ij}^+ is the average path weight of the axons from v_i to the endbulbs (or synaptic knobs) N_{ij}, and β_i^+ is a scaling parameter which transforms potentials into frequencies. The signal (1) travels along the axons e_{ij}^+ at a finite velocity and reaches the endbulbs N_{ij} at time t; it thereupon activates the excitatory transmitter production process $z_{ij}(t)$ taking place in N_{ij}, and an average amount of excitatory transmitter equal to

$$T_{ij}(t) = F_{ij}(t)[z_{ij}(t)-\Omega_{ij}^+]^+ \tag{2}$$

is instantaneously released from N_{ij} into the synaptic clefts between N_{ij} and the postsynaptic cell bodies v_j. The excitatory transmitter in (2) thereupon changes the average postsynaptic potential $x_j(t)$ of v_j.

The amount of change in the average postsynaptic potential $x_j(t)$ due t the average excitatory transmitter $T_{ij}(t)$ depends on whether or not $x_j(t$ has a fixed finite maximum M_j and a fixed finite minimum m_j. Throughou this paper, we assume that M_j and m_j exist. Then the simplest equation for the change in $x_j(t)$ due to the input signal $T_{ij}(t)$ alone is

$$\dot{x}_j(t) = \alpha_j^+[M_j - x_j(t)][\gamma_j^+ + T_{ij}(t)] - \alpha_j^-\gamma_j^-[x_j(t) - m_j], \tag{3}$$

where the initial data of (3) satisfies the inequalities

$$m_j \leq x_j(t) \leq M_j, \tag{4}$$

and thus, by (3), (4) holds for all $t \geq 0$.

The equilibrium potential P_j of $x_j(t)$ is defined as that value of $x_j(t)$ in (3) which follows by setting

$$\dot{x}_j(t) = T_{ij}(t) = 0.$$

We find that

$$P_j = \frac{\alpha_j^+\gamma_j^+ M_j + \alpha_j^-\gamma_j^- m_j}{\alpha_j^+\gamma_j^+ + \alpha_j^-\gamma_j^-}. \tag{5}$$

The equilibrium potential P_i of $x_i(t)$ and the spiking threshold Γ_{ij}^+ of e_{ij}^+ are constrained by the inequality

$$\Gamma_{ij}^+ > P_i, \tag{6}$$

which prevents spikes from entering the axons e_{ij}^+ unless $x_i(t)$ strictly exceeds its equilibrium potential by at least the amount $\Gamma_{ij}^+ - P_i$.

The excitatory transmitter production process $z_{ij}(t)$ in the endbulbs N_{ij} is controlled jointly by the average spiking frequency $F_{ij}(t)$ which impinges on N_{ij} at time t, and by the postsynaptic potential $x_j(t)$ of v_j through the quantity

$$R_j(t) \equiv [x_j(t) - \Lambda_j^+]^+. \tag{7}$$

This varies linearly with $x_j(t)$ up to a threshold cut-off at the value Λ_j^+. The simplest equation for $z_{ij}(t)$ in the case of a fixed finite maximum M_{ij} and a fixed finite minimum m_{ij} existing for $z_{ij}(t)$ is given by

$$\dot{z}_{ij}(t) = [M_{ij} - z_{ij}(t)][u_{ij}^+ + \gamma_{ij}^+ F_{ij}(t)R_j(t)] - u_{ij}^-[z_{ij}(t) - m_{ij}], \tag{8}$$

where

$$m_{ij} \leq z_{ij}(0) \leq M_{ij}. \tag{9}$$

The equilibrium value Q_{ij} of $z_{ij}(t)$ is found by setting

$$\dot{z}_{ij}(t) = F_{ij}(t)R_j(t) = 0$$

in (8). We find that

$$Q_{ij} = \frac{u_{ij}^+ M_{ij} + u_{ij}^- m_{ij}}{u_{ij}^+ + u_{ij}^-}, \tag{10}$$

unless $u_{ij}^+ = u_{ij}^- = 0$.

The equilibrium value Q_{ij} in (10) and the threshold value Ω_{ij}^+ of $z_{ij}(t)$ in (2) are constrained by the inequality

$$\Omega_{ij}^+ \geq Q_{ij}, \tag{11}$$

which guarantees that the signal $T_{ij}(t)$ from v_i to v_j at time t equals zero, unless $z_{ij}(t)$ exceeds its equilibrium value.

(8) consists of two main terms. The term

$$u_{ij}^+[M_{ij} - z_{ij}(t)] - u_{ij}^-[z_{ij}(t) - m_{ij}] \tag{12}$$

describes the spontaneous approach of $z_{ij}(t)$ to its equilibrium value Q_{ij}. The crucial term

$$\gamma_{ij}^+[M_{ij} - z_{ij}(t)]F_{ij}(t)R_j(t) \tag{13}$$

describes how the network learns from the inputs to which it is exposed. The term $[M_{ij} - z_{ij}(t)]$ in (13) merely guarantees in (8) that $z_{ij}(t)$ never exceeds M_{ij}, and that $z_{ij}(t)$'s response to $F_{ij}(t)R_j(t)$ is approximately linear for small values of $z_{ij}(t)$. The term $F_{ij}(t)R_j(t)$ controls all the learning undergone by $z_{ij}(t)$. In particular, if $z_{ij}(t)$ initially satisfies the inequality

$$z_{ij}(0) \leq Q_{ij}, \tag{14}$$

then one readily finds by (8) that z_{ij} always satisfies this inequality, and thus $T_{ij}(t) \equiv 0$, unless $F_{ij}(t)R_j(t)$ becomes positive at some time $t \geq 0$. Consequently, if (14) holds, an input to v_i cannot create an output from v_j via a signal along e_{ij}^+ unless $F_{ij}(t)R_j(t)$ has previously been positive. $F_{ij}(t)R_j(t)$ can be made positive by presenting large inputs to v_i and then v_j with a time separation of approximately τ_{ij} time units; that is, by 'teaching' the network the transition from v_i to v_j.

Because the growth of $z_{ij}(t)$ above equilibrium depends on the product $T_{ij}(t)R_j(t)$, we say that $z_{ij}(t)$ cross-correlates $T_{ij}(t)$ and $R_j(t)$, or that the correlation of presynaptic and postsynaptic influences within the endbulb determines the level of transmitter production therein.

Heuristically speaking, $z_{ij}(t)$ grows quickly only if both $x_i(t - \tau_{ij}^+)$ and $x_j(t)$ are large. Choosing Γ_{ij}^+ as in (6) guarantees that $T_{ij}(t)$ is large only if $x_i(t - \tau_{ij}^+)$ has been excited by presynaptic excitatory inputs to suprathreshold (and in particular supraequilibrium) values. In a similar fashion, we constrain the threshold Λ_j^+ in (7) by the inequality

$$\Lambda_j^+ \geq P_j, \tag{15}$$

to guarantee that $R_j(t)$ is large only if $x_j(t)$ has been excited by postsynaptic excitatory inputs to supra-equilibrium values.

The psychological basis for assuming that transmitter production is controlled by the cross-correlation of presynaptic and postsynaptic influences is given in Grossberg (1969*a*,*b*) and is briefly reviewed in Grossberg (1968). In this context we merely accept this fact as given and explore its qualitative neural consequences.

3. Antagonism between Na^+ and K^+

In general, both excitatory and inhibitory signals can perturb $x_j(t)$ at any time (Grossberg, 1969*b*). Then (3) is generalized by

$$\dot{x}_j(t) = \alpha_j^+[M_j - x_j(t)][\gamma_j^+ + J_j^+(t) + I_j^+(t)] - \alpha_j^-[x_j(t) - m_j][\gamma_j^- + J_j^-(t) + I_j^-(t)], \quad (16)$$

where $J_j^+(t)$ is the sum of excitatory signals received at time t from other cell bodies v_m, $J_j^-(t)$ is the sum of inhibitory signals received at time t from other cell bodies v_m, $I_j^+(t)$ is a known excitatory signal—controlled, say, by an experimentalist in the outside world—and $I_j^-(t)$ is a know inhibitory signal. Sections 20 and 21 of Grossberg (1969*b*) exploit the obvious formal symmetry between excitatory and inhibitory terms in (16) to replace the equation (16) for $x_j(t)$ by a pair of equations for new variables $x_j^+(t)$ and $x_j^-(t)$ which are antagonistically coupled at suprathreshold values. The simplest such equations which are compatible with (16) are given by

$$\dot{x}_j^{+}(t) = \alpha_j^{+\,+}[M_j^+ - x_j^+(t)][\gamma_j^{+\,+} + J_j^{+\,+}(t) + I_j^{+\,+}(t)] - \alpha_j^{+\,-}\gamma_j^{+\,-}[x_j^+(t) - m_j^+], \quad (17)$$

$$\dot{x}_j^{-}(t) = \alpha_j^{-\,+}\gamma_j^{-\,+}[M_j^- - x_j^-(t)] - \alpha_j^{-\,-}[x_j^-(t) - m_j^-][\gamma_j^{-\,-} + J_j^{-\,-}(t) + I_j^{-\,-}(t)], \quad (18)$$

and

$$\chi\{[x_j^+(t) - \Gamma_{ji}^{+\,-}]^+\}\{\beta_j^{+\,-}[x_j^+(t) - \Gamma_{ji}^{+\,-}]^+ - \beta_j^{-\,-}[\Gamma_j^{-\,+} - x_j^-(t)]^+\} = 0, \quad (19)$$

where

$$\chi(w) = \begin{cases} 1, & w > 0 \\ 0, & w \leq 0. \end{cases}$$

Grossberg (1969*b*) interprets these equations to mean that excitatory transmitter received by v_j at time t causes an inward flux of $x_j^+(t)$ which induces an outward flux of $x_j^-(t)$ at suprathreshold values, whereas inhibitory transmitter received by v_j at time t causes only an outward flux of $x_j^-(t)$. This asymmetry in the response of $x_j^+(t)$ and $x_j^-(t)$ to excitatory and inhibitory transmitters can be traced to the excitatory bias created by the thresholds appearing in $T_{ij}(t)$ in (3) and in $F_{ij}(t)R_j(t)$ in (8). The excitatory bias is, in turn, needed in order that the network be able to learn.

Grossberg (1969*b*) identifies (qualitatively) $x_j^+(t)$ with the amount of unbound Na^+ within v_j and $x_j^-(t)$ with the amount of unbound K^+ within v_j. Then (17) to (19) claim that excitatory transmitter (say ACh) creates an inward flux of Na^+ which, in turn, at suprathreshold values creates an outward flux of K^+, whereas inhibitory transmitter creates only an outward flux of K^+. The familiar asymmetry of Na^+ and K^+ fluxes in response to excitatory and inhibitory transmitters is thus linked to the network's

ability to learn. The following sections will suggest further consequences for learning of this asymmetry in a discussion of the production of excitatory transmitters.

4. Coupling of K^+ to ACh Release

The term $F_{ij}(t)$ in (1) is replaced in the passage from (16) to (17) — (19) by

$$F_{ij}^{+\,+}(t) = \beta_i^{+\,+}[x_i^+(t - \tau_{ij}^{+\,+}) - \Gamma_{ij}^{+\,+}]^+ p_{ij}^{+\,+}, \quad (20)$$

which is interpreted to mean that spikes along the axon occur when inward fluxes of Na^+ induce outward fluxes of K^+. This is in qualitative accord with well-known data (Ruch, Patton, Woodburg & Towe, 1961; Hodgkin, 1964).

The term $T_{ij}(t)$ in (2) must be similarly transformed to

$$T_{ij}^{+\,+}(t) = F_{ij}^{+\,+}(t)[z_{ij}^{+\,+}(t) - \Omega_{ij}^{+\,+}]^+, \quad (21)$$

where $z_{ij}^{+\,+}(t)$ in (21) replaces $z_{ij}(t)$ in (8) as a symbol for excitatory transmitter. Three facts guide the physical interpretation of (21):

(a) $F_{ij}^{+\,+}(t)$ describes an influx of Na^+ and an outflux of K^+ at the endbulb $N_{ij}^{+\,+}$ at time t;
(b) $z_{ij}^{+\,+}(t)$ describes the production of excitatory transmitter within $N_{ij}^{+\,+}$ at time t;
(c) $T_{ij}^{+\,+}(t)$ describes the average amount of excitatory transmitter released from $N_{ij}^{+\,+}$ at time t.

Given (a) to (c), (21) shows that increasing the outward flux of K^+ from $N_{ij}^{+\,+}$ also increases the outward flux of excitatory transmitter (say ACh). There is, indeed, experimental evidence that K^+ concentration and ACh release are coupled (Hebb & Kryjević, 1962; Hutter & Kostial, 1955; Liley, 1956). (21) also suggests a coupling between inward flux of Na^+ and outward flux of ACh. Since this coupling is apparently merely an indirect coupling via K^+, it need not appear at all in the absence of an action potential. Some evidence has been found which suggests the existence of a link between Na^+ concentration and ACh release (Birks, 1965; Fatt & Katz, 1952*a*,*b*), but this link has also been thought to be weak, if at all relevant (Hutter & Kostial, 1955).

5. Learning Requires No Fewer than Two Pairs of Ions (Na^+, K^+, Ca^{++}, Mg^{++})

We now transform (8) to an equation for excitatory transmitter $z_{ij}^{+\,+}(t)$. Part of this task is very simple. Indeed, all appearances of $z_{ij}(t)$ in (8) must be replaced by $z_{ij}^{+\,+}(t)$; all coefficients must be correspondingly labeled by

a pair of extra superscripts '$^{++}$', and $F_{ij}(t)$ must be replaced by $F_{ij}^{++}(t)$, as defined in (20), since $F_{ij}(t)$ describes the effect of presynaptic spiking on N_{ij}, which we have interpreted to be the result of coupled inward and outward Na^+ and K^+ fluxes, respectively. Then (8) becomes

$$\dot{z}_{ij}^{++}(t) = [M_{ij}^{++} - z_{ij}^{++}(t)][u_{ij}^{+++} + \gamma_{ij}^{++} F_{ij}^{++}(t) R_j(t)] - u_{ij}^{++-}[z_{ij}^{++}(t) - m_{ij}^{++}]. \tag{22}$$

It remains only to interpret the term $R_j(t)$. The following considerations guide us in this task.

$z_{ij}^{++}(t)$ describes a process going on within N_{ij}^{++}, and $x_j(t)$ describes a process going on within v_j. Since the rate of change of $z_{ij}^{++}(t)$ depends on $R_j(t)$, $R_j(t)$ must represent a quantity (or quantities) whose size is controlled by v_j, which is transported across the synapse for use within N_{ij}^{++}.

To determine what this quantity is, note first that $F_{ij}^{++}(t)$ represents a pair of antagonistic ionic fluxes within N_{ij}^{++} at time t, and second that $R_j(t)$ interacts with these fluxes as in the term $F_{ij}^{++}(t)R_j(t)$ of (22) to control $z_{ij}^{++}(t)$'s rate of change. It is therefore strongly suggested that $R_j(t)$ also represents a pair of antagonistic ionic fluxes.

The simplest choice of ions for $R_j(t)$ is, of course, Na^+ and K^+. We therefore examine the possibility that $R_j(t)$ should be replaced by

$$R_j^+(t) = [x_j^+(t) - \Lambda_j^{++}]^+ \tag{23}$$

in (22). We will now show, however, that if $R_j^+(t)$ replaces $R_j(t)$ in (22), then the resulting equation

$$\dot{z}_{ij}^{++}(t) = [M_{ij}^{++} - z_{ij}^{++}(t)][u_{ij}^{+++} + \gamma_{ij}^{++} F_{ij}^{++}(t) R_j^+(t)] - u_{ij}^{++-}[z_{ij}^{++}(t) - m_{ij}^{++}] \tag{24}$$

cannot be given a sensible physical interpretation. Just as $F_{ij}^{++}(t)$ in (20) describes an influx of Na^+ and an outflux of K^+ within N_{ij}^{++} at time t, $R_j^+(t)$ in (23) describes an influx of Na^+ and an outflux of K^+ within v_j at time t. (24) describes the effects of these fluxes on $z_{ij}^{++}(t)$, a process which is going on within N_{ij}^{++}. In particular, the process $z_{ij}^{++}(t)$ is influenced only by those aspects of the $R_j^+(t)$ fluxes which have some effect on the N_{ij}^{++} membrane. These effects are a decrease in Na^+ and an increase in K^+ at the exterior of the N_{ij}^{++} membrane. But $F_{ij}^{++}(t)$ has essentially the same effects on the exterior of the N_{ij}^{++} membrane, and in any case $F_{ij}^{++}(t)$ and $R_j^+(t)$ both involve the same ionic species. How then can it be that these expressions determine $z_{ij}^{++}(t)$ in (24) only through their product? In particular, by (24), $z_{ij}^{++}(t)$ cannot grow in response to even an enormous $F_{ij}^{++}(t)$ value if $R_j^+(t) = 0$, even though $F_{ij}^{++}(t)$ provides within the interior of N_{ij}^{++} all the ionic effects which $R_j^+(t)$ possibly can. The replacement of $R_j(t)$ in (22) by $R_j^+(t)$ is therefore inadmissible.

Our previous arguments strongly suggest, however, that $R_j(t)$ represents some pair of antagonistic ions. Since these ions cannot be Na^+ and K^+ if (22) is to hold even approximately, we must seek another pair of ions which could be represented by $R_j(t)$. Fortunately the biochemical literature abounds in examples in which the ions Na^+ and K^+ interact with other ionic species. In many situations (Dixon & Webb, 1958), the divalent ions Ca^{++} and Mg^{++} are found along with Na^+ and K^+. It is therefore not implausible to assume on general grounds that $R_j(t)$ is realized by an antagonism between the divalent ions Ca^{++} and Mg^{++}. It remains only to decide whether Ca^{++} or Mg^{++} increases as $R_j(t)$ increases. In many biochemical reactions, Na^+ and Ca^{++} act synergistically (Fruton & Simmonds, 1958). Since the interaction between the ion pairs (Na^+, K^+) and (Ca^{++}, Mg^{++}) is represented by the expression $F_{ij}^{++}(t)R_j(t)$, and since an increase in $F_{ij}^{++}(t)$ designates an increase in Na^+, we suppose that an increase in $R_j(t)$ designates an increase in Ca^{++}. We have thus been led by simple steps to the idea that the interaction $F_{ij}^{++}(t)R_j(t)$, which determines the learning processes within our networks, is realized by the interaction of two pairs of antagonistic ions within the end-bulbs. We now derive several of the consequences of this plausible labeling of our variables, and collect data from a variety of sources which seem to be compatible with these consequences.

6. Binding of Na^+ and Ca^{++} as Synergistic Cofactors on Production Sites of Excitatory Transmitter

Consider the term

$$\gamma_{ij}^{++}[M_{ij}^{++} - z_{ij}^{++}(t)]F_{ij}^{++}(t)R_j(t) \tag{25}$$

in (22), which describes learning within our networks. We now give (25) a qualitative neural interpretation. Let

M_{ij}^{++} = the total number of intra-N_{ij}^{++} sites at which excitatory transmitter can be produced,

and

$z_{ij}^{++}(t)$ = the total number of active sites at which excitatory transmitter is produced at time t.

Then

$M_{ij}^{++} - z_{ij}^{++}(t)$ = the total number of inactive excitatory transmitter production sites at time t,

and

(22) states that the rate at which inactive sites become active at time t is jointly proportional to the number of inactive sites at time t and the product $F_{ij}^{++}(t)R_j(t)$.

New transmitter production sites are created by the interaction in (25) at time t only if both $F_{ij}^{++}(t)$ and $R_j(t)$ are positive; that is, only if supra-equilibrium quantities of Na^+ and Ca^{++} are made available at the inactive intra-N_{ij}^{++} transmitter production sites due to prior presynaptic and postsynaptic excitation. In other words, *inactive excitatory transmitter production sites (or enzymes) are activated by the binding to these sites (or enzymes) of* Na^+ *and* Ca^{++} *as synergistic cofactors.* (See, for example, Dixon & Webb (1958) and Vallee (1960) for a discussion of cofactors.)

Although this conclusion arises in a simple way from our theoretical methods, it represents a phenomenon which will be very difficult to measure directly in the laboratory, since it discusses combinations of bound ions on a continually varying number of active intra-endbulb sites. Nonetheless, there exists a considerable amount of indirect experimental evidence which is compatible with this conclusion.

A main new idea is that joint inward Na^+ and Ca^{++} fluxes are created by endbulb excitation and thereupon stimulate transmitter production, whereas K^+ and Mg^{++} are antagonists to Na^+ and Ca^{++} in this role. Such fluxes have, indeed, been experimentally reported (del Castillo & Engbaek, 1954; Eccles, 1964; Harvey & MacIntosh, 1940; Hodgkin & Keynes, 1954; Hutter & Kostial, 1954). Just as inward fluxes of Na^+ and Ca^{++} presumably facilitate transmitter production, it is natural to expect that such fluxes facilitate transmitter release. In particular, choosing ACh as our excitatory transmitter, we are led to expect that reducing the Ca^{++} concentration in the medium bathing N_{ij}^{++} should lead to a reduction in ACh output for a fixed excitation of N_{ij}^{++}. Since Mg^{++} is presumably a Ca^{++} antagonist in transmitter production, it is also natural to expect Mg^{++} to be a Ca^{++} antagonist in controlling the amount of ACh release. These expectations have also been experimentally reported (del Castillo & Engbaek, 1959; Hutter & Kostial, 1954; Jenkinson, 1957).

7. A Hierarchy of Intracellular Ionic Binding Strengths

Another indirect piece of confirmatory experimental evidence is gleaned from the following observation. New intra-endbulb transmitter production sites are activated only when both $F_{ij}^{++}(t)$ and $R_j(t)$ are positive, which means that supraequilibrium quantities of Na^+ and Ca^{++} are made available to these sites. When equilibrium is restored, $F_{ij}^{++}(t)$ and $R_j(t)$ become zero, which means that the high intra-endbulb concentrations of Na^+ and Ca^{++} are eliminated. Nonetheless, the rate of change $\dot{z}_{ij}^{++}(t)$ of $z_{ij}^{++}(t)$ in (22) due to the term (25) is also zero when equilibrium is restored. In other words, the endbulb 'remembers' how much transmitter it must produce. Of course (22) also describes a possible spontaneous decay term

$$u_{ij}^{++}[M_{ij}^{++} - z_{ij}^{++}(t)] - u_{ij}^{++-}[z_{ij}^{++}(t) - m_{ij}^{++}],$$

but this expression is not coupled to the ionic fluxes that characterize equilibrium, and can therefore be thought of as a slowly varying (perhaps zero) leakage term.

The following basic questions hereby arise. How can high concentrations of Na^+ and Ca^{++} jointly activate a process which maintains its activity even after the concentrations of these ions are reduced at equilibrium? Otherwise expressed, what keeps $z_{ij}^{++}(t)$ at the high values needed to produce a memory of past events even when the sources of these high values are removed as equilibrium is restored? In particular, why doesn't the high intra-endbulb K^+ concentration at equilibrium reversibly inhibit $z_{ij}^{++}(t)$ growth, just as Na^+ and Ca^{++} excited $z_{ij}^{++}(t)$ growth at nonequilibrium?

Since $z_{ij}^{++}(t)$ does maintain the high values acquired during nonequilibrium, and joint coupling of Na^+ and Ca^{++} causes these values, we are forced into the following conclusion: the Na^+ and Ca^{++} ions which activated the transmitter production sites are not removed from the endbulb when equilibrium is restored. In other words, a fraction of the free Na^+ and Ca^{++} ions which enter the endbulb during excitation is bound on intra-endbulb transmitter production sites, and this binding is so strong that it cannot be displaced by the return of a high intra-endbulb K^+ concentration as equilibrium is restored. In particular, the intracellular K^+ ions are not so strongly bound. We are hereby led to expect that most of the intracellular K^+ exists in unbound form, whereas higher proportions of intracellular Na^+ and/or Ca^{++} exist in bound form. These expectations have been experimentally reported (Brink, 1954; Ussing, 1960).

It is of singular importance to realize that the asymmetry within the coupling of Na^+ to K^+ at the cell membrane in response to external excitatory and inhibitory inputs is required in order to guarantee asymmetric binding properties of Na^+ and K^+ within the cell interior.

8. The Control of Cellular Production Rates by Ions: Strength of Binding versus Ion Availability

The above remarks suggest a qualitative answer to a special case of the following important general question: how do cells 'know' how much of a given quantity to produce in response to external environmental demands? Since the postulates which led to our equations are quite general (Grossberg, 1968), it may well be that some qualitative features of our answer generalize to other cases in which a cell's external environment dictates some of its

production levels. We therefore summarize some features of our answer in more general terms.

Our point of departure is the hypothesis that ions such as Na^+ and Ca^{++}, which presumably activate intra-endbulb sites (or enzymes) with considerable vigor, are kept substantially out of the endbulb during equilibrium. Only in nonequilibrium periods such that $x_i^+(t-\tau_{ij}^{++}) > \Gamma_{ij}^{++}$ and $x_j(t) > \Lambda_j^+$ can these ions penetrate the membrane *en masse* to initiate higher levels of intra-endbulb transmitter production. Since equilibrium time intervals can, in principle, exceed nonequilibrium time intervals by a very large numerical factor, the ions Na^+ and Ca^{++} which bind most strongly at M_{ij}^{++} sites are available least frequently within the endbulb. In other words, the process of synergistic (Na^+, Ca^{++}) binding to M_{ij}^{++} sites, having a limited opportunity to occur, is made effective by guaranteeing that whenever the opportunity does occur, the process takes place vigorously and its effects are long-lasting; cf. Brink (1954) and Quastel (1962).

These facts suggest the following general heuristic scheme for integrating equilibrium and non-equilibrium phases in the life of a cell, which subsumes the problem of rendering the cell responsive to fluctuations in its external environment. The argument can be broken into three main steps.

8.1. COEXISTENCE OF EQUILIBRIUM AND EVOLUTION

An equilibrium phase of a cell can, in principle, be characterized by particular values of prescribed cellular parameters. For example, the equilibrium of a nerve cell can be characterized by the membrane concentrations of such parameters as Na^+ and K^+. Suppose that a cell exists whose equilibrium is characterized by particular values of all of its parameters. Such a cell 'forgets' all non-equilibrium values of its parameters when it returns to equilibrium. In particular, the equilibrium of such a cell cannot coexist with long-term responses of the cell to brief changes in its external environment. For convenience, we henceforth call such long-term responses evolutionary trends.

Certainly not all cells are of this type. Brains can learn! Henceforth we concern ourselves only with cells whose equilibrium phase can coexist with an evolutionary trend. We denote such a cell by C. By definition, the equilibrium phase of C does not require a specification of values for all cellular parameters. It suffices to specify the values of a fraction of these parameters. We denote these equilibrium parameters collectively by E. A particular evolutionary trend in C requires the specification of values for parameters which we denote by N. Since the parameters N control an evolutionary trend, they need not always take on the same values when the parameters E take on equilibrium values.

8.2. THE EXTERNAL ENVIRONMENT PERTURBS THE EQUILIBRIUM PARAMETERS

The external environment communicates its demands upon C by changing the values of parameters at C's periphery, or membrane. These parameters are, however, often the parameters E, since equilibrium is a state of C which is characterized by a particular choice of external environment. For example, a nerve cell returns to equilibrium when all excitatory and inhibitory inputs are zero. We conclude that the external environment often induces an evolutionary trend in the parameters N by perturbing the parameters E. The parameters E must therefore faithfully communicate to the parameters N the demands of the external environment. We are hereby led to the following basic but ostensible paradox: If the parameters E faithfully communicate to the parameters N the external environmental demands that signal an evolutionary trend, then why don't the parameters E also faithfully communicate to the parameters N the external environmental demands that signal equilibrium, and thereby eradicate the evolutionary trend in N whenever equilibrium is restored?

8.3. THE EQUILIBRIUM VALUES COMPETE WITH THE NON-EQUILIBRIUM VALUES OF THE EQUILIBRIUM PARAMETERS

Given the natural assumption that the parameters E pass on faithfully to N all states of the external environment, the following resolution of this paradox seems inevitable: The equilibrium values of E do not eradicate the evolutionary trend in N because they cannot dislocate from N the non-equilibrium values of E that induced the trend. In the case that the parameters E are realized by ions, this means that a hierarchy of ionic binding strengths exists at the intracellular sites (or enzymes) which alter intracellular production in response to extracellular demands. The ions which are most available during equilibrium are bound least strongly to these sites. The ions which are introduced at these sites by the extracellular demands are strongly bound as synergistic cofactors to these sites, and thereby activate them.

Proceeding in the reverse direction, suppose that the ions which bind most strongly to these sites are not substantially kept out of the cell during equilibrium, and are allowed to bind freely with these sites and thereby to activate them. Then essentially all sites will always be occupied, and the production rate at these sites will always be in a state of equilibrium, albeit a very active equilibrium. The evolutionary trend is thus destroyed.

9. The Mitochondrion and Ion Translocation

Given the hypothesis that Na^+ and Ca^{++} are synergistic cofactors in the activation of sites that contribute to transmitter production, it is desirable to find candidates for these sites. A cellular system which seems to have a

strong affinity for Na^+ and Ca^{++} is the mitochondrion (Lehninger, 1965), whose importance as the 'power plant' of aerobic cells has attracted much attention in recent years. Here, we merely indicate some relevant data concerning the mitochondrion so that the reader can qualitatively appreciate the similarities between this data and the predictions made above. The following quotation from Lehninger (1965, pp. 169–71) is of particular interest.

"Carafoli and Rossi have carried out a complete analysis of the movement of the major cations and anions into and out of rat liver mitochondria during respiration; they did so in order to establish the interrelationships of these movements. The mitochondria were incubated in a medium containing respiratory substrate, phosphate, Cl^-, Na^+, K^+, Mg^{++}, Ca^{++} and ATP. The results are given in Figure (. . . 2, figure number mine) which shows the ionic composition

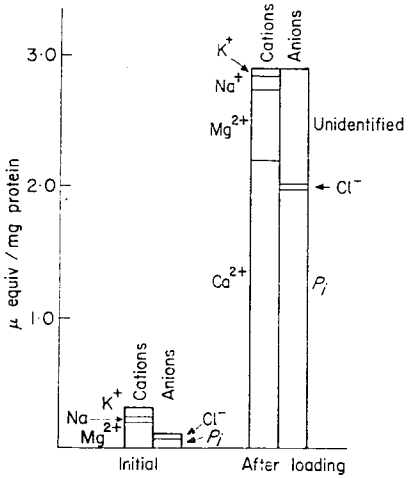

FIG. 2

before and after the incubation. The fresh mitochondria show the occurrence of K^+ and Mg^{++} as the major cations, with only very low amounts of Na^+ and Cl^-, ... However, the fully loaded mitochondria, after incubation, showed not only a strikingly large uptake of Ca^{++} and phosphate, but also a significant change in the pattern of Mg^{++}, Na^+, K^+ and Cl^-."

Inspection of Fig. 2 shows that the transition from the 'initial' column to the 'after-loading' column involves an increase in both the ratios Na^+/K^+ and Ca^{++}/Mg^{++}, which is compatible with our theoretical expectations.

To the extent that this data is an example of our theoretical expectations, then ion translocation in neural mitochondria can be interpreted as a means for setting mitochondrial reaction rates at a level commensurate with the intensity and duration of a positively polarized non-equilibrium excitation phase. These rates endure long into the equilibrium phase.

10. Provision of ATP for Synaptic Vesicles by Mitochondria

Suppose that ion translocation in the mitochondrion is indeed an example of the synergism between Na^+ and Ca^{++} that contributes to transmitter production. Then mitochondria should be found clustered near regions of high transmitter density. Histological evidence suggests that transmitter is stored in synaptic vesicles, and that mitochondria can be found clustered near these vesicles (de Robertis, 1964, p. 32 and micrographs throughout the book). Perhaps the activated mitochondria supply the ATP needed to produce acetyl coenzyme A, which in turn presumably reacts with choline under the aegis of the enzyme choline acetylase to produce acetylcholine (Fruton & Simmonds, 1958).

11. Contiguity of Synaptic Vesicles and the Synaptic Cleft

The histological investigations (Eccles, 1964; de Robertis, 1964) which have revealed the existence of synaptic vesicles also show that these vesicles are often clustered most densely along the endbulb surface which faces the synaptic cleft. This location is certainly well chosen for a vesicle whose supposed role is expeditiously to release transmitter into the synaptic cleft to excite the post-synaptic membrane. Yet how does the vesicle know how to choose this useful location? Such knowledge must seem mysterious to any theory which holds that transmitter production depends only on the past excitation history of the presynaptic nerve which contains the transmitter, since the excitation of just this nerve does not provide any information concerning the exact location of the synaptic cleft relative to the endbulb membrane. Indeed, such a theory might well be forced to predict that transmitter vesicles are found uniformly throughout the endbulb, or closer to the presynaptic source of excitation than to the synaptic cleft, or at best with uniform density along all endbulb surfaces.

The preferential location of synaptic vesicles near the synaptic cleft is qualitatively easily understood in the present theory, using the fact that transmitter production depends both on presynaptic and postsynaptic influences. Presumably the postsynaptic ionic influence is carried over the synaptic cleft to the presynaptic endbulb, so that the region most likely

to have all the ingredients needed for transmitter production lies nearest the synaptic cleft. It is also qualitatively clear why the postsynaptic ionic influence does not spread evenly throughout the presynaptic endbulb. This is because the large Na^+ and Ca^{++} concentrations near the synaptic cleft are presumably bound within the endbulb as soon as they reach an appropriate site, which will most likely be at their point of entry. Moreover, the amount of Ca^{++} entering the cell cannot be so large as to uniformly saturate all sites within the endbulb, or else the desired evolutionary trend will be destroyed, as we observed at the end of section 8. Hence the additional Ca^{++} provided by the postsynaptic cell is preferentially bound near the synaptic cleft, and thus the synaptic vesicles are created where they are most needed.

12. Binding of Mg^{++} by RNA in the Cell Nucleus

The large quantities of Ca^{++} needed for synergistic binding of Na^+ and Ca^{++} in N_{ij}^{++} are released into the synaptic cleft facing N_{ij}^{++} when the postsynaptic cell v_j is excited above the Λ_j^+ threshold. This Ca^{++} enters N_{ij}^{++} along with Na^+ only when N_{ij}^{++} is presynaptically excited as well. Otherwise, much of the Ca^{++} in the synaptic cleft is presumably reabsorbed into v_j.

This argument fails completely if N_{ij}^{++} can provide as much Ca^{++} as v_j, given a fixed level of excitation, since then $F_{ij}^{++}(t)$ would stand for essentially the same ionic fluxes as $R_j(t)$, and the coupling $F_{ij}^{++}(t)R_j(t)$ of (22) could not be realized, using the argument of section 5. Since v_j presumably can supply more Ca^{++} than N_{ij}^{++}, we must find a rationale for this fact.

Given that $R_j(t)$ represents an antagonism between Ca^{++} and Mg^{++}, the fact that Ca^{++} is released when v_j is excited means that Mg^{++} is needed by v_j during excitation. A structure must therefore exist within v_j—which is not found in N_{ij}^{++}—and which selectively binds Mg^{++} ions when v_j is active, and whose binding with Mg^{++} is preferred to (or antagonized by) binding with Ca^{++}. It must be clearly realized that this argument does not mean that no Ca^{++} is provided by N_{ij}^{++}, but only that more Ca^{++} is provided by v_j. In a similar fashion, the fact that presynaptic excitation at N_{ij}^{++} induces coupled Na^+ and K^+ fluxes does not imply that such fluxes are absent from postsynaptic excitation at v_j.

The cell body v_j certainly has at least one very prominent structure which the endbulb N_{ij}^{++} does not have, namely the cell nucleus. If this is the structure being sought, then the cell nucleus ought to selectively bind Mg^{++} ions when the cell body is activated. Among the most plentiful constituents of the cell nucleus are the nuclear RNA's. It is also known that RNA activity depends sensitively on Mg^{++} concentration (Spirin, 1964; Boedtker, 1960; Watson, 1965).

13. Interaction of Neural Excitation and RNA

Suppose, indeed, that the nuclear RNA's are among the structures that we are seeking to bind Mg^{++}. We must therefore also claim that a vigorous excitation of a nerve cell by transmissions from other nerve cells will cause systematic variations in the nuclear RNA's. Such variations have been found experimentally (Hamberger & Hyden, 1963; Hyden, 1962; Koenig, 1964).

From the present theoretical perspective, these variations presumably reflect provisions made by the nucleus to compensate for metabolic drains and other demands associated with the excitation, for example by activating the RNA's which control protein synthesis (Watson, 1965; de Robertis, 1965).

Once experiments were produced demonstrating variations in RNA activity in learning situations, several authors proposed that individual RNA strands coded the content of the learning in some fashion, and that one could, in principle, recover the content of whole segments of learned experiences in such a strand if one but had the key for decoding its structure. This view seems to be incorrect from the present perspective. The RNA's seem to be needed merely to keep the cell at production levels appropriate to the level of excitation by the external environment. Memories of psychological events are, it would seem, spread over large collections of cells (Grossberg, 1969*a*,*b*).

14. Transport Down the Axon

The hypothesis that Mg^{++} is bound to nuclear molecules is further strengthened by the following observation. Consider Fig. 3.

Figure 3 schematically represents a presynaptic nerve cell with nucleus N_i whose excitatory endbulb N_{ij}^{++} impinges upon the postsynaptic nerve cell v_j with nucleus N_j. We have concluded that N_j selectively binds Mg^{++}

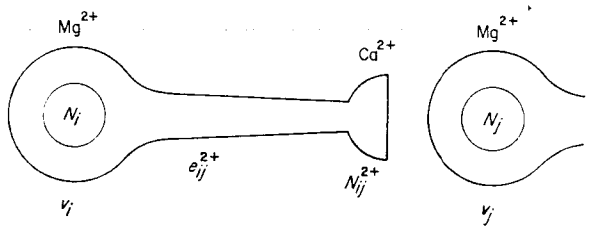

FIG. 3

in order to free Ca^{++} for binding within N_{ij}^{++} when both N_{ij}^{++} and v_j are vigorously excited. If v_i and v_j are of the same cell type, then Mg^{++}-must also be selectively bound by N_i when v_i is vigorously excited. Since v_i is connected to N_{ij}^{++} by the axon e_{ij}^{++}, we must prevent most of the molecules which bind Mg^{++} within v_i from flowing down the axon to N_{ij}^{++}, or else N_{ij}^{++} will have too many Mg^{++}-binding molecules. Thus at least part of the Mg^{++} must be bound within v_i to structures which are so large or so well cemented within v_i that they are never carried down the axon to the endbulb. Heavy macromolecules within N_i, such as the RNA's, are likely candidates for such a role.

On the other hand, whenever v_i is excited to suprathreshold values, then the axon e_{ij}^{++} and the endbulb N_{ij}^{++} are also excited. The axon and the endbulb must be able to recover from this excitation. The postulated mechanism of recovery is activation by Mg^{++} of the RNA's during excitation, leading to higher rates of protein synthesis, etc. However, the RNA's are substantially localized within the cell body v_i. Thus the molecules produced by RNA activation, after being produced in v_i, must be able to travel down the axon to the endbulb where they will be needed to guarantee recovery from excitation. These molecules therefore might well be lighter than the more immobile RNA's, and they might well be bound to less Mg^{++} than is bound to the activated RNA's. Experiments have been performed which find a transport of material from the cell body along the axon to the endbulb (Friede, 1959; Koenig, 1958; Ochs & Burger, 1958; Waelsch & Lajtha, 1960; Weiss & Hiscoe, 1946).

15. Faithful Transport by Na^+ and K^+ of Information down the Axon

How does the nucleus know how many recovery molecules will be needed by the axon and the endbulb? A qualitative, but rather speculative, answer to this question is easily given. Our equations suggest that the suprathreshold amount of membrane excitation at v_i is linearly coupled to the amount of Mg^{++} made available at nuclear sites, and this in turn is presumably linearly coupled to the number of recovery molecules which are produced. On the other hand, (1) shows that the law governing axonal transmission at suprathreshold values is also linearly coupled to membrane excitation at v_i. Hence the number of recovery molecules which are produced is roughly proportional to the amount of excitation within the axon and endbulb, and is thus of the right order of magnitude to guarantee that recovery does occur.

These speculations provide some further insight into the desirability of carrying signals down the axon using travelling waves of excitation whose

frequency faithfully mirrors the magnitude of excitation at the cell body, as in (1). Two advantages are hereby gained:

(a) the signals received by N_{ij}^{++} from e_{ij}^{++} faithfully reproduce the level of excitation of v_i, and therefore carry the 'information' from v_i to N_{ij}^{++} without bias;

(b) the level of excitation of v_i alone gives the nucleus an accurate picture of how many recovery molecules will be needed by the entire nerve cell.

16. Why Nerve Cells are not Spherical: the Intimate Bond between Neural Geometry and Neural Dynamics

It is practically a truism that the simplest geometrical objects are as homogeneous and as symmetric as possible. Thus, among the simplest three-dimensional and finite bodies are the spheres, and it is useful to think of the complexity of a three-dimensional and finite body—such as a nerve cell—in terms of its deviations from sphericity. It is also natural to suppose that a finite system in nature will assume the simplest shape that is compatible with its function. We are then readily led to ask: What features of a nerve cell's functions require that it be non-spherical?

Our speculations suggest how the role of nerve cells as mechanisms of learning requires their non-spherical shape. We link a nerve cell's ability to learn with the existence of different chemical affinities at two opposite poles of the nerve cell, namely at the cell body and at the endbulbs; that is, the nerve cell is a kind of chemical dipole. Were the nerve cell spherical in all ways, in particular with a spherical nucleus in its center, then symmetry arguments would readily imply that this chemical dipole could not be realized.

Given the need for a dipole shape, the nerve cell is then confronted with the formidable problem of carrying signals from its external environment reliably from one end of the dipole to the other. This problem is formidable precisely because the functional biases caused by the dipole might well be expected to distort the signal as it travels along the cell. Our speculations suggest that the cell has solved this problem in the following ingenious—but intuitively simple—way. The signals from the external environment, which naturally enough must first perturb the boundary, or membrane, of the cell, are transmitted reliably from one end of the dipole to the other along this boundary, whereas the chemical dipole properties of the cell are safely ensconsed well within the cellular interior, where they can secondarily benefit from external environmental news without profoundly distorting the transmission of this news along the entire cell.

A closed boundary which carries an environmental signal reliably from one end of a dipole to the other must surely have translational symmetry,

and still be as spherical as possible for simplicity. The cylindrical shape of axons realizes both of these requirements.

Since the two ends of the dipole contain the extra chemical machinery which realizes the dipole, they must generally be broader than the axon. In order that learned 'choices' be possible within a neural network, a single cell body must often be touched by several endbulbs or must send out signals to several endbulbs. In either case, the cell body must contain enough chemical machinery to fulfil its end of the chemical dipole with each of these endbulbs. Hence, the cell body is generally larger than the endbulb. The main qualitative geometrical features of Fig. 3 are thus obvious consequences of our dynamical picture of the process of learning. More intricate geometrical arrangements, such as dendritic and axonal branching, and variations in cell body shape can also be qualitatively understood on psychological grounds as forthcoming papers of this series will show.

17. Membrane Area, Nuclear Volume and the Endoplasmic Reticulum

We now discuss further details of the interaction between postsynaptic cell body membrane and postsynaptic nucleus due to excitation of presynaptic endbulbs. This interaction presumably tells the nucleus how many recovery molecules to produce to offset the debilitating effects of membrane excitation throughout the cell. Thus there must exist enough nuclear matter to accurately discriminate the total amount of membrane excitation. The following paragraphs discuss a simple way to guarantee this need, and refer to compatible data or alternatively: to data compatible with our conclusions.

Consider an idealized cell C with cell body membrane M and nucleus N. Denote the portion of M which is contiguous to some endbulb by M_E. Cells *in vivo* are certainly more complicated than the cell C to be described, but a clear-cut idealization provides a firm base over which to erect realistic qualifications. The following assumptions are made concerning C:

(a) on the average, the total excitation received by M is proportional to the area of M_E;

(b) the area of M_E is proportional to the area of M.

(a) and (b) imply

(c) on the average, the total excitation received by M is proportional to the area of M.

The next hypothesis states that N can discriminate the total excitation of M:

(d) the number of molecules in N which interact with M is proportional to the average total excitation of M.

If we assume that

(e) the total number of molecules in N which interact with M is proportional to the total volume of N, then by (c), (d) and (e), we find

(f) the area of M is proportional to the volume of N.

Bok (1959) has presented data which confirms (f). He contrasts this data with data from the cells of other animal organs whose nuclear volume is proportional to the volume of the cell body, rather than to its surface area. From this he concludes that signals to the nerve cell membrane play an important role in regulating the internal life of the cell, as indeed we are arguing in somewhat greater detail.

(f) is based on several speculative, but simple, steps. The rationale for these steps breaks down completely unless M and N interact with each other along a direct pathway. The existence of such a pathway is strongly suggested by the importance of the M–N interaction to cellular dynamics. On the other hand, this interaction is certainly not the only one needed to sustain a living cell. In particular, the directness of the M–N interaction is limited by the cytoplasm through which it must pass. Thus a dilemma arises: How can the M–N interaction be direct if the cytoplasm supports many other cellular functions which can, in principle, perturb this interaction?

This dilemma is readily overcome if tubules carry the interaction through the cytoplasm between a small portion of M and a corresponding portion of N, as in Fig. 4. Then unrelated cytoplasmic mechanisms can be bypassed entirely, and the directness of M–N interaction is restored. Without such tubules, the total number and complexity of cytoplasmic mechanisms that could exist without destroying the M–N interaction might well be so limited that the resultant cell would be doomed by an insurmountable evolutionary disadvantage.

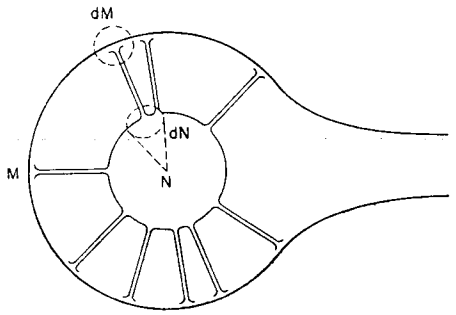

FIG. 4

Extensive tubular connections that are intimately related to M and N are indeed known, and seem to be vital to the biochemical organization of the cell (de Robertis, Nowinski & Saez, 1965; Sjöstrand, 1964). They form part of the endoplasmic reticulum.

18. Spatial Self-similarity, Cell Type and Control

This section shows that the areas of the cell body membrane and the axonal membrane are proportional in the idealized cell C of the previous section. The following additional assumption which is tacitly assumed in section 15, is made concerning C:

(g) the number of recovery molecules produced by C is proportional to the number of membrane-activated molecules in N.

(c), (d) and (g) imply

(h) the total number of recovery molecules produced by C is proportional to the area of M.

We also assume

(i) the total number of molecules used per unit time in the recovery of a membrane region R is proportional to the area of R.

(h) and (i) imply the important conclusion

(j) a fixed fraction θ_M of recovery molecules—which is independent of the area of M—is used in the recovery of M.

Denoting the remainder of C's membrane by M′, (j) implies

(k) a fixed fraction $\theta_{M'} = 1-\theta_M$ of recovery molecules—which is independent of the area of M′—is used in the recovery of M′.

Since the area of M′ is primarily devoted to the axon A of C, the following conclusion holds approximately:

(l) a fixed fraction of recovery molecules is used in the recovery of A.

(f), (h) and (l) imply the important conclusion

(m) the area of A is proportional to the area of M and to the volume of V.

From (m), we readily conclude that a small cell C_1 of type C gives rise to a large cell C_2 of type C simply by blowing up all dimensions of C_1 by a multiplicative constant. We now reverse this procedure and define a cell type C by the requirement that all members of the type are dilations or

contractions of each other by a multiplicative factor, as depicted in Fig. 5. Such a collection of cells is said to be spatially self-similar. Spatial self-similarity is thus a geometrical counterpart of the dynamic requirement that the nucleus be able to provide for the needs of the entire cell. Such a basic dynamic demand ought to be compatible with many examples in nature, and the reader can easily list a number of familiar biological shapes which are either spatially self-similar or have iterated branches which are spatially self-similar (e.g. small versus large leaves and the branching of veins in leaves).

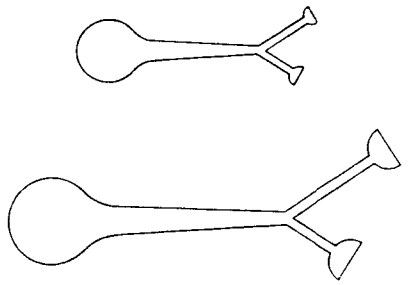

FIG. 5

The members of a cell type C differ by variations in only one parameter. This parameter can, in principle, be controlled by a single gene G_C in the nuclei of the cells of this type. In other words, a suitable change in the activity of G_C can transform any member of the cell type into any other. Since this concept of cell type arises by considering the interaction of membrane excitation with the nucleus, it is only a step to the idea that the level of membrane excitation can control the activity of G_C, and thereby change the size of the cell. This suggestion gains added plausibility when we recall that the M–N interaction describes an accurate control of internal ion concentrations by membrane events. A very high level of prolonged membrane excitation can destroy physiologically useful concentrations unless the cell increases in size to compensate. In a cell with many specialized functions, it is clearly inefficient to increase the size of cell mechanisms which are unrelated to the M–N interaction. It is known, however, that mitochondria can be made to swell by the addition of ions such as Ca^{++} (Lehninger, 1965).

A forthcoming paper will use the principle of sufficient reason to derive an extension of spatial self-similarity, namely spatio-temporal self-similarity, which has some nontrivial experimental consequences.

19. Tubules Along the Axon

In section 14, we concluded that recovery molecules are transported from the nucleus to the axon and endbulbs. This transport process must occur without distortion over long cellular distances. Hence section 18 suggests that it is accomplished by tubules from the nucleus which end along the axon and endbulb, as shown in Fig. 6. The existence of tubules along the axon has indeed been reported (de Robertis *et al.*, 1965, p. 409).

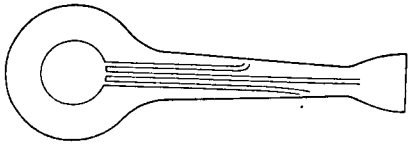

FIG. 6

Given the complexity of living cells, it is unlikely that these tubules perform only the above-mentioned function. Suppose for example that presynaptic endbulb excitation of a given cell heightens the production of some of the material needed for learning at the postsynaptic endbulb. Consider the network of Fig. 7, in which the cells at the end of each v_i

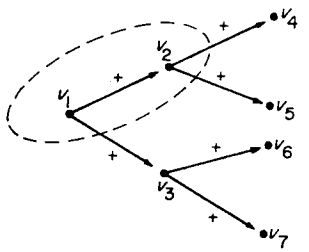

FIG. 7

initially receive equal excitation from their common source. Let the transition from v_1 to v_2 be learned by creating successive inputs at v_1 and v_2. v_2 then produces new material needed for learning in N_{24}^{++} and N_{25}^{++}, which is transported along the tubules of e_{24}^{++} and e_{25}^{++}. Learning at a future time of a transition from v_2 to v_4 or v_5 is thus easier than learning of a transition from v_3 to v_6 or v_7. That is, the establishment of previous links in the chain of associations might well help to prepare for the establishment of the next link in the chain.

20. Two Main Steps in Transmitter Production

Each psychological act is the net effect of many individual neural events averaged together. Since the postulates used in Grossberg (1968) to derive our equations are psychological, the variables appearing in these equations are also the net effect of many neural events averaged together. We now derive some of the finer steps in transmitter production that are averaged together in these variables. This is done by showing that the single variable $z_{ij}^{++}(t)$ actually represents two processes taking place at two different rates. These two processes are the following ones.

(a) *Slowly varying transmitter production rates.* All 'memories' of past events in our networks are contained within the $z_{ij}^{++}(t)$ functions of (22). These functions therefore vary more slowly than the events themselves; i.e. more slowly varying than the $x_i^+(t-\tau_{ij}^{++})$ and $x_j(t)$ functions.

(b) *Rapidly varying transmitter release.* $T_{ij}^{++}(t)$ in (21) is the average amount of excitatory transmitter released per unit time from N_{ij}^{++} into the synaptic clefts which face v_j. $T_{ij}^{++}(t)$ is rapidly varying—compared to $z_{ij}^{++}(t)$ at least—because $T_{ij}^{++}(t)$ is a linear function of $x_i^+(t-\tau_{ij}^{++})$ at suprathreshold values.

The physical interpretation of $T_{ij}^{++}(t)$ leads us to the two processes represented by $z_{ij}^{++}(t)$. $T_{ij}^{++}(t)$ is the product of presynaptic spiking frequency $F_{ij}^{++}(t)$ and of

$$G_{ij}^{++}(t) \equiv [z_{ij}^{++}(t)-\Omega_{ij}^{++}]^+,$$

which is the total amount of transmitter in N_{ij}^{++} that can be released from N_{ij}^{++} at time t. Since $G_{ij}^{++}(t)$ is a linear function of $z_{ij}^{++}(t)$ at suprathreshold values, and since the amount $T_{ij}^{++}(t)$ of $G_{ij}^{++}(t)$ leaves N_{ij}^{++} at time t, then should not $z_{ij}^{++}(t)$ decrease at the rate $T_{ij}^{++}(t)$? That is, should not $T_{ij}^{++}(t)$ be subtracted from the right-hand side of (22)? On formal grounds, this subtraction procedure is inadmissible, because then $z_{ij}^{++}(t)$ would be reduced drastically in size whenever the presynaptic spiking frequency $F_{ij}^{++}(t)$ momentarily became large, and the 'memory' within $z_{ij}^{++}(t)$ would quickly be destroyed. If subtraction of $T_{ij}^{++}(t)$ is inadmissible, then how can $G_{ij}^{++}(t)$ be a linear function of $z_{ij}^{++}(t)$ at suprathreshold values?

Only one answer is available to us: $G_{ij}^{++}(t)$ and $z_{ij}^{++}(t)$ represent two different processes. The $G_{ij}^{++}(t)$ process has the two properties that:

(i) $G_{ij}^{++}(t)$ is linearly coupled to $z_{ij}^{++}(t)$ whenever $z_{ij}^{++}(t) > \Omega_{ij}^{++}$;
(ii) the amount $T_{ij}^{++}(t)$ of $G_{ij}^{++}(t)$ leaves N_{ij}^{++} at time t.

The properties (i) and (ii) can coexist if and only if the amount $T_{ij}^{++}(t)$ of transmitter lost from N_{ij}^{++} is instantaneously replenished until $G_{ij}^{++}(t)$ is once again linearly coupled to $z_{ij}^{++}(t)$; that is, if and only if the rate of

replenishment is infinite. Obviously this rate seems to be infinite because replenishment occurs rapidly compared to the time scale of our psychologically derived equations. We now refine the time scale of these equations by assuming that the rate of replenishment is finite. Then a new variable $Z_{ij}^{+\,+}(t)$, distinct from $z_{ij}^{+\,+}(t)$, must be introduced to stand for the total amount of transmitter within $N_{ij}^{+\,+}$ at time t.

In terms of $Z_{ij}^{+\,+}(t)$ and $z_{ij}^{+\,+}(t)$, (i) becomes the statement that $Z_{ij}^{+\,+}(t)$ seeks a level proportional to $z_{ij}^{+\,+}(t)$. In other words, there exist times t for which

$$Z_{ij}^{+\,+}(t) \cong \delta_{ij} z_{ij}^{+\,+}(t), \tag{26}$$

where δ_{ij} is a positive constant. These are the times t before which $Z_{ij}^{+\,+}(t)$ is not depleted by being released from $N_{ij}^{+\,+}$. By this hypothesis, $Z_{ij}^{+\,+}(t)$ attains the asymptote $\delta_{ij} z_{ij}^{+\,+}(t)$ at a finite rate. Thus, at every time t for which no transmitter leaves $N_{ij}^{+\,+}$,

$$\dot{Z}_{ij}^{+\,+}(t) = \lambda_{ij}^{+}[\delta_{ij} z_{ij}^{+\,+}(t) - Z_{ij}^{+\,+}(t)], \tag{27}$$

where

$$0 \leq Z_{ij}^{+\,+}(t) < \delta_{ij} z_{ij}^{+\,+}(t),$$

and λ_{ij}^{+} is a positive constant.

If an amount $W_{ij}^{+\,+}(t)$ does leave $N_{ij}^{+\,+}$ at time t, then $Z_{ij}^{+\,+}(t)$ in (27) is diminished by the amount $W_{ij}^{+\,+}(t)$. Thus in general,

$$\dot{Z}_{ij}^{+\,+}(t) = \lambda_{ij}^{+}[\delta_{ij} z_{ij}^{+\,+}(t) - Z_{ij}^{+\,+}(t)] - W_{ij}^{+\,+}(t). \tag{28}$$

$W_{ij}^{+\,+}(t)$ cannot be identified with $T_{ij}^{+\,+}(t)$ in (21) because $G_{ij}^{+\,+}(t)$ no longer represents the total releasable transmitter in $N_{ij}^{+\,+}$ at time t. Guided by (21) and (26), we replace $G_{ij}^{+\,+}(t)$ in $T_{ij}^{+\,+}(t)$ by

$$H_{ij}^{+\,+}(t) \equiv [Z_{ij}^{+\,+}(t) - U_{ij}^{+\,+}]^{+} \tag{29}$$

in $W_{ij}^{+\,+}(t)$, where

$$U_{ij}^{+\,+} = \delta_{ij} \Omega_{ij}^{+\,+}. \tag{30}$$

Thus $W_{ij}^{+\,+}(t)$ in (28) equals

$$W_{ij}^{+\,+}(t) = \lambda_{ij}^{-} F_{ij}^{+\,+}(t) H_{ij}^{+\,+}(t), \tag{31}$$

where λ_{ij}^{-} is a positive constant. (28) and (31) together replace (1) and (2). Heuristically speaking, this replacement merely exchanges a process with an infinite reaction rate for a qualitatively identical process with a finite reaction rate. in this sense, the passage from (1) and (2) to (28) and (30) refines the time scale of our system of equations.

In (28) and (31),

$Z_{ij}^{+\,+}(t)$ = total amount of available transmitter in $N_{ij}^{+\,+}$ at time t,

and

$z_{ij}^{+\,+}(t)$ = total activity of the transmitter production process in $N_{ij}^{+\,+}$ at time t (e.g. total number of active transmitter-producing sites).

In the special case that the transmitter is acetylcholine (ACh), then

$Z_{ij}^{+\,+}(t)$ = total amount of available ACh in $N_{ij}^{+\,+}$ at time t,

and

$z_{ij}^{+\,+}(t)$ = total activity at time t of the choline acetylase system (ChAc) which controls ACh production (Fruton & Simmonds, 1958; Krnjević, 1965; Sumner & Somers, 1953).

21. Feedback Inhibition

Equation (28) has the following chemical interpretation. Let the right-hand side of (28) be written as a sum of three terms

$$\dot{Z}_{ij}^{+\,+}(t) = A_{ij}(t) + B_{ij}(t) + C_{ij}(t), \tag{32}$$

where

$$A_{ij}(t) = \lambda_{ij}^{+} \delta_{ij} z_{ij}^{+\,+}(t), \tag{33}$$

$$B_{ij}(t) = -\lambda_{ij}^{+} Z_{ij}^{+\,+}(t), \tag{34}$$

and

$$C_{ij}(t) = -W_{ij}^{+\,+}(t). \tag{35}$$

(32) and (33) mean that the rate of transmitter production at time t is proportional to the number of active transmitter producing sites at time t, while (32) and (34) mean that the rate of transmitter production at time t is diminished by an amount proportional to the amount of transmitter at time t. This decrease in transmitter production due to available transmitter is needed to guarantee that $Z_{ij}^{+\,+}(t)$ seeks a level proportional to $z_{ij}^{+\,+}(t)$. Otherwise the level of $Z_{ij}^{+\,+}(t)$ would grow to infinity. The combined effects of (33) and (34) on (32) are diagrammed schematically in Fig. 8.

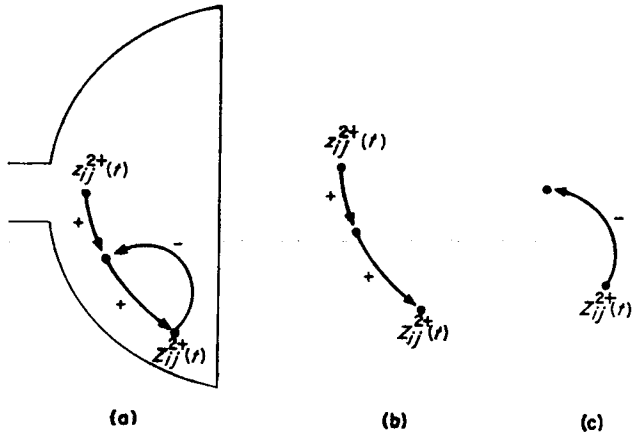

FIG. 8

Figure 8(a) describes the combined effects of (33) and (34). Figure 8(b) describes only the effect of (33). The directed chain of arrows with '+' signs designates that an increase in $z_{ij}^{+\,+}(t)$ causes an increase in $Z_{ij}^{+\,+}(t)$. Figure 8(c) describes only the effect of (34). The directed arrow with a '−' sign designates than an increase in $Z_{ij}^{+\,+}(t)$ causes a decrease in some prior stage of transmitter production. This prior stage cannot be the $z_{ij}^{+\,+}(t)$ stage itself, because $z_{ij}^{+\,+}(t)$ is a slowly varying memory function that is not perturbed by rapid fluctuations in $Z_{ij}^{+\,+}(t)$. In other words, there exists a feedback inhibition by the transmitter endproduct $Z_{ij}^{+\,+}(t)$ of a prior stage of transmitter production. This inhibition cannot influence those sites controlling transmitter production which are activated by extracellular demands without destroying the cellular memory of these demands. Hence a later stage in the chain of reactions leading to transmitter production is inhibited by the endproduct. Feedback inhibition by endproducts on a precursor stage of endproduct production is a familiar biochemical mechanism (Fruton & Simmonds, 1958; Wyatt, 1964). The need for this inhibition to act at an intermediate stage of production, rather than at an initial stage, is in the present context clear-cut. $z_{ij}^{+\,+}(t)$ is a slowly varying process and $Z_{ij}^{+\,+}(t)$ is a rapidly varying process. Inhibition by $Z_{ij}^{+\,+}(t)$ of $z_{ij}^{+\,+}(t)$ would make $z_{ij}^{+\,+}(t)$ rapidly varying as well, and would thereby destroy the stability of control by the external environment of the amount of $Z_{ij}^{+\,+}(t)$ to be produced.

The term (35) in (32) can now be understood as a reduction in feedback inhibition of transmitter production due to release from $N_{ij}^{+\,+}$ of the amount $W_{ij}^{+\,+}(t)$ of transmitter at time t. Figure 8 can therefore be extended to Fig. 9, in which the dotted arrow with a '+' sign signifies that the release of transmitter from $N_{ij}^{+\,+}$ reduces the amount of feedback inhibition by $Z_{ij}^{+\,+}(t)$

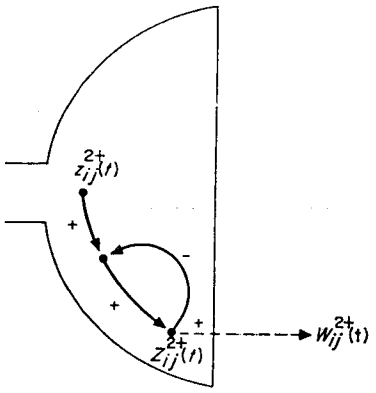

FIG. 9

on the rate of $Z_{ij}^{+\,+}(t)$ production. Figure 9 itself can be augmented by including the x_i^+ and x_i^- arrows that couple to $Z_{ij}^{+\,+}$ and $z_{ij}^{+\,+}$ fluxes, as in Fig. 10. The arrows and vertices in Fig. 10 are not drawn at their positions within the endbulb, but merely schematize the direction of the interactions. Figure 10 illustrates the exquisite balance of excitatory and inhibitory factors that controls production and release of chemical transmitters within our systems.

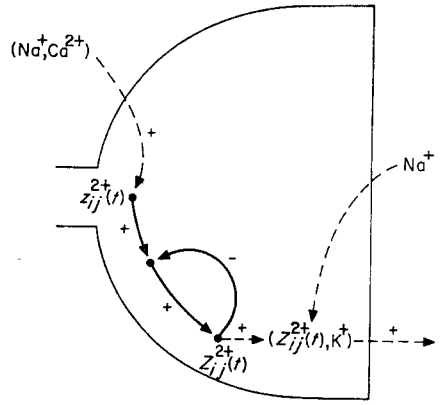

FIG. 10

22. Excitatory Transients in Transmitter Release

Passing from (1) and (2) to (28) and (31) has some interesting new consequences. Suppose, for example, that no presynaptic spiking has occurred for a long time prior to time $t = 0$, and that a steady-state spiking level is instantaneously turned on in the time interval $t \geq 0$. We will show that an excitatory transient in transmitter release is thereby created, which then gradually sinks at an exponential rate to a steady state level of transmitter release. Such an excitatory transient has been experimentally reported (Eccles, 1964).

By hypothesis,

$$F_{ij}^{+\,+}(t) = \begin{cases} 0, & t < 0 \\ F, & t \geq 0 \end{cases} \tag{36}$$

where F is a positive constant. By (36), $W_{ij}^{+\,+}(t) = 0$, $t < 0$, so that (27) holds for $t < 0$. We can therefore assume that $Z_{ij}^{+\,+}(t)$ has attained the level $\delta_{ij}^{+\,+} z_{ij}^{+\,+}(t)$ by time $t = 0$; that is,

$$Z_{ij}^{+\,+}(0) = \delta_{ij} z_{ij}^{+\,+}(0). \tag{37}$$

Since $Z_{ij}^{++}(t)$ fluctuates more rapidly than $z_{ij}^{++}(t)$, and we are studying the transient behavior of $Z_{ij}^{++}(t)$, we assume that $z_{ij}^{++}(t)$ remains essentially constant; that is,

$$z_{ij}^{++}(t) \cong z_{ij}^{++}(0)$$

for all $t \geq 0$ in the transient phase of $Z_{ij}^{++}(t)$'s response to $F_{ij}^{++}(t)$. Then (28) becomes

$$\dot{Z}_{ij}^{++}(t) \cong \lambda_{ij}^{+}[\delta_{ij} z_{ij}^{++}(0) - Z_{ij}^{++}(t)] - \lambda_{ij}^{-} F_{ij}^{++}(t)[Z_{ij}^{++}(t) - U_{ij}^{++}]^{+}, \quad (38)$$

subject to (36) and (37). To avoid trivialities, let F be sufficiently large to keep $Z_{ij}^{++}(t)$ larger than U_{ij}^{++}. Then (38) becomes

$$\dot{Z}_{ij}^{++}(t) \cong \lambda_{ij}^{+}[\delta_{ij} z_{ij}^{++}(0) - Z_{ij}^{++}(t)] - \lambda_{ij}^{-} F_{ij}^{++}(t)[Z_{ij}^{++}(t) - U_{ij}^{++}], \quad (39)$$

which is a linear equation in $Z_{ij}^{++}(t)$ whose solution is readily found to be

$$Z_{ij}^{++}(t) \cong \delta_{ij} z_{ij}^{++}(0)\left\{e^{-a_{ij}(F)t} + \frac{b_{ij}(F)}{a_{ij}(F)}[1 - e^{-a_{ij}(F)t}]\right\}, \quad (40)$$

for $t \geq 0$, where

$$a_{ij}(F) = \lambda_{ij}^{+} + \lambda_{ij}^{-} F$$

and

$$b_{ij}(F) = \lambda_{ij}^{+} + \lambda_{ij}^{-} F\left(\frac{\Omega_{ij}^{++}}{z_{ij}^{++}(0)}\right).$$

Since

$$z_{ij}^{++}(0) > \Omega_{ij}^{++}, \qquad b_{ij}(F) < a_{ij}(F).$$

Thus, by (40), $Z_{ij}^{++}(t)$ decays at an exponential rate $a_{ij}(F)$ from the initial value $\delta_{ij} z_{ij}^{++}(0)$ to the final value

$$Z_{ij}^{++}(\infty) \equiv \delta_{ij} z_{ij}^{++}(0) b_{ij}(F)/a_{ij}(F). \quad (41)$$

The average rate of transmitter release from N_{ij}^{++} at time t is readily found from (31) and (40) after some algebraic manipulation. It is

$$W_{ij}^{++}(t) = \delta_{ij}\lambda_{ij}^{-}\left[\frac{\lambda_{ij}^{+} + \lambda_{ij}^{-} F e^{-a_{ij}(F)t}}{\lambda_{ij}^{+} + \lambda_{ij}^{-} F}\right][z_{ij}^{++}(0) - \Omega_{ij}^{++}]F, \quad (42)$$

for $t \geq 0$. By (42), $W_{ij}^{++}(t)$ jumps from 0 to

$$W_{ij}^{++}(0) \equiv \delta_{ij}\lambda_{ij}^{-}[z_{ij}^{++}(0) - \Omega_{ij}^{++}]F \quad (43)$$

at time zero, and then decays at an exponential rate to the asymptotic value

$$W_{ij}^{++}(\infty) \equiv \frac{\delta_{ij}\lambda_{ij}^{-}\lambda_{ij}^{+}[z_{ij}^{++}(0) - \Omega_{ij}^{++}]F}{\lambda_{ij}^{+} + \lambda_{ij}^{-} F}. \quad (44)$$

We diagram $W_{ij}^{++}(t)$ in Fig. 11. The initial peak in the graph of $W_{ij}^{++}(t)$ is called an excitatory transient. Such transients are familiar both in the release of chemical transmitters and in other transport processes which are influenced by chemical accumulation during rest intervals (Eccles, 1964; Ratliff, 1965).

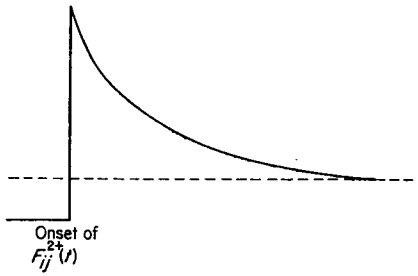

FIG. 11

23. Steady-state Total Transmitter versus Released Transmitter as Functions of Spiking Frequency

We now contrast the asymptotic total available transmitter $Z_{ij}^{++}(\infty)$ with the fraction $W_{ij}^{++}(\infty)$ of this transmitter which is released as functions of steady-state spiking frequency F. By (41),

$$Z_{ij}^{++}(\infty) = \delta_{ij}\left[\frac{\lambda_{ij}^{+} z_{ij}^{++}(0) + \lambda_{ij}^{-}\Omega_{ij}^{++}F}{\lambda_{ij}^{+} + \lambda_{ij}^{-} F}\right]. \quad (45)$$

Since $z_{ij}^{++}(0) > \Omega_{ij}^{++}$, $Z_{ij}^{++}(\infty)$ is a monotone decreasing function of F; that is, increasing F depletes the total steady-state amount of available transmitter. On the other hand, by (44), $W_{ij}^{++}(\infty)$ is a monotone increasing function of F; that is, as the steady-state spiking frequency increases, the steady-state amount of transmitter which is released per unit time also increases. The total amount of transmitter in N_{ij}^{++} and the amount of this transmitter which is released thus do not co-vary as functions of F. This fact is qualitatively confirmed by experiments (Friede, 1959).

For small values of F, (44) shows that

$$W_{ij}^{++}(\infty) \cong \lambda_{ij}^{-}\{\delta_{ij}[z_{ij}^{++}(0) - \Omega_{ij}^{++}]\}F, \quad (46)$$

which is a linear function of F, just as $T_{ij}^{++}(\infty)$ in (20) is. $W_{ij}^{++}(\infty)$ differs qualitatively from $T_{ij}^{++}(\infty)$ as a function of F only in that $W_{ij}^{++}(\infty)$ saturates at the value

$$\delta_{ij}\lambda_{ij}^{+}[z_{ij}^{++}(0) - \Omega_{ij}^{++}]$$

as F approaches infinity, whereas $T_{ij}^{++}(\infty)$ is a linear function of F for all values of F.

24. Post-tetanic Potentiation

(44) and (46) are merely first approximations to the steady-state values of total transmitter released in response to a given level, F, of presynaptic spiking. This is because we have fixed $z_{ij}^{++}(t)$ at the constant value $z_{ij}^{++}(0)$

for all $t \geq 0$ in all of our estimates. This approximation is reasonable only for presynaptic spiking bursts of short duration, because $z_{ij}^{+\,+}(t)$ is a slowly varying function. For presynaptic spiking bursts of long duration, the variation of $z_{ij}^{+\,+}(t)$ cannot be ignored. Indeed, the variation of $z_{ij}^{+\,+}(t)$ in response to long bursts of presynaptic spiking has effects which strikingly resemble the experimental phenomenon of post-tetanic potentiation (Eccles, 1957) as we now show.

$z_{ij}^{+\,+}(t)$ is described by equation (22), with $F_{ij}^{+\,+}(t)$ replaced by F, as in (36). That is,

$$\dot{z}_{ij}^{+\,+}(t) = [M_{ij}^{+\,+} - z_{ij}^{+\,+}(t)][u_{ij}^{+\,+} + \gamma_{ij}^{+\,+} F R_j(t)] - u_{ij}^{+\,+}[z_{ij}^{+\,+}(t) - m_{ij}^{+\,+}], \quad (47)$$

with $z_{ij}^{+\,+}(0)$ chosen greater than $\Omega_{ij}^{+\,+}$ to avoid trivialities. $R_j(t)$ in (47) is also a function of F, which is determined in the following way. For simplicity, suppose that $W_{ij}^{+\,+}(t)$ is the only input that perturbs v_j. Then replacing $T_{ij}^{+\,+}(t)$ by its finite-rate analog $W_{ij}^{+\,+}(t)$ in (16) we find

$$\dot{x}_j(t) = \alpha_j^+[M_j - x_j(t)][\gamma_j^+ + W_{ij}^{+\,+}(t)] - \alpha_j^- \gamma_j^-[x_j(t) - m_j],$$

which by (36) equals

$$\dot{x}_j(t) = \alpha_j^+[M_j - x_j(t)]\{\gamma_j^+ + \lambda_{ij}^- F[Z_{ij}^{+\,+}(t) - U_{ij}^{+\,+}]\} - \alpha_j^- \gamma_j^-[x_j(t) - m_j]. \quad (48)$$

$Z_{ij}^{+\,+}(t)$ in (48) is, in turn, a solution of (28), which in the present case becomes

$$\dot{Z}_{ij}^{+\,+}(t) = \lambda_{ij}^+[\delta_{ij} z_{ij}^{+\,+}(t) - Z_{ij}^{+\,+}(t)] - \lambda_{ij}^- F[Z_{ij}^{+\,+}(t) - U_{ij}^{+\,+}]. \quad (49)$$

Since $Z_{ij}^{+\,+}(t)$ varies much more rapidly than $z_{ij}^{+\,+}(t)$, we can suppose that $Z_{ij}^{+\,+}(t)$ quickly attains the value prescribed by $z_{ij}^{+\,+}(t)$ and F in (49) before $z_{ij}^{+\,+}(t)$ varies significantly. (49) then implies the approximate identity

$$Z_{ij}^{+\,+}(t) \cong \delta_{ij}\left[\frac{\lambda_{ij}^+ z_{ij}^{+\,+}(t) + \lambda_{ij}^- \Omega_{ij}^{+\,+} F}{\lambda_{ij}^+ + \lambda_{ij}^- F}\right],$$

which is simply (45) with $z_{ij}^{+\,+}(0)$ replaced by $z_{ij}^{+\,+}(t)$. Then by a similar modification of (44), (48) becomes approximately

$$\dot{x}_j(t) \cong \alpha_j^+[M_j - x_j(t)]\left\{\gamma_j^+ + \frac{\delta_{ij}\lambda_{ij}^-\lambda_{ij}^+[z_{ij}^{+\,+}(t) - \Omega_{ij}^{+\,+}]F}{\lambda_{ij}^+ + \lambda_{ij}^- F}\right\} - \alpha_j^- \gamma_j^-[x_j(t) - m_j]. \quad (50)$$

It is clear by inspection of (47) and (50) that $z_{ij}^{+\,+}(t)$ is a monotone increasing function of F once initial transients in $Z_{ij}^{+\,+}(t)$ die out. $z_{ij}^{+\,+}(t)$ is a strictly monotone increasing function of F only if F is sufficiently large to drive $x_j(t)$ above Λ_j^+, and thus to make $R_j(t)$ positive in (47).

This conclusion has the following effect. Consider two copies M_1 and M_2 of the network M depicted in Fig. 12. In M_1, let a prolonged interval of

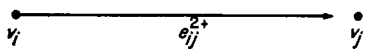

FIG. 12

intense presynaptic spiking from v_i be followed after a brief rest interval by a short presynaptic volley from v_i. In M_2, only the short volley occurs. In both M_1 and M_2, $Z_{ij}^{+\,+}(t)$ can quickly recover from prior depletion before the short volley occurs. The asymptote $\delta_{ij} z_{ij}^{+\,+}(t)$ which $Z_{ij}^{+\,+}(t)$ seeks in M_1 is, however, higher than the asymptote sought in M_2. The short volley in M_1 will therefore release a larger amount of transmitter from $N_{ij}^{+\,+}$ in M_1 than in M_2, and consequently $x_j(t)$ will thereafter become larger in M_1 than in M_2. The asymptote $\delta_{ij} z_{ij}^{+\,+}(t)$ of $Z_{ij}^{+\,+}(t)$ increases slowly and steadily as the duration and intensity of presynaptic spiking increases. This effect is in sharp contrast to the excitatory transient of Fig. 11, which is rapidly depleted by prolonged presynaptic spiking. This slow build-up in synaptic firing strength has many qualitative features of post-tetanic potentiation (Eccles, 1957). It is quite feasible that this potentiation mechanism combines with the presynaptic mechanism depicted in Fig. 7.

25. Transmitter Mobilization

Figure 11 shows that the release of transmitter from $N_{ij}^{+\,+}$ in response to presynaptic spiking is instantaneous. On the other hand, our theoretical picture requires that the production of transmitter occurs within the endbulb interior, albeit in a region close to the synapse. The instantaneous release of transmitter therefore requires the motion of transmitter to the synapse at an infinite velocity. Surely this requirement is but an approximation to events which occur at a finite velocity. The instantaneous approximation is due to the coarseness of the psychological time scale in which we derived our equations, as was the instantaneous replenishment of transmitter.

We must therefore seek equations which do not change the qualitative effects of the instantaneous process but which nonetheless replace infinite velocities by finite velocities. To do this, we again need two variables instead of one. The first variable is just

$Z_{ij}^{+\,+}(t)$ = the total amount of transmitter in $N_{ij}^{+\,+}$ at time t.

The second variable must be

$\tilde{Z}_{ij}^{+\,+}(t)$ = the total amount of transmitter in $N_{ij}^{+\,+}$ which is at the membrane facing the synaptic cleft at time t.

In other words,

$\tilde{Z}_{ij}^{+\,+}(t)$ = the total amount of mobilized transmitter in $N_{ij}^{+\,+}$ at time t.

A process of transmitter mobilization has indeed been experimentally recorded (Eccles, 1964).

Clearly the total amount of transmitter which is released from N_{ij}^{++} at time t is no longer $W_{ij}^{++}(t)$, since only transmitter which has reached the membrane at time t can be released at time t. The amount of transmitter which is released at time t is defined by analogy with $W_{ij}^{++}(t)$ in (31) and (29) by

$$\tilde{W}_{ij}^{++}(t) = \lambda_{ij}^{-} F_{ij}^{++}(t)[\tilde{Z}_{ij}^{++}(t) - U_{ij}^{++}]^{+}. \tag{51}$$

It remains only to determine how transmitter is mobilized for release by presynaptic spikes. Two alternatives arise: the rate of mobilization is either independent of spiking frequency, or increases as spiking frequency increases. We will consider the former alternative explicitly. The latter alternative can readily be handled once the former is discussed. Among the simplest equations expressing this alternative are

$$\dot{Z}_{ij}^{++}(t) = \lambda_{ij}^{+}[\delta_{ij} z_{ij}^{++}(t) - \tilde{Z}_{ij}^{++}(t)] - \lambda_{ij}^{-} F_{ij}^{++}(t)[\tilde{Z}_{ij}^{++}(t) - U_{ij}^{++}]^{+}, \tag{52}$$

and

$$\dot{\tilde{Z}}_{ij}^{++}(t) = \omega_{ij}^{+}[Z_{ij}^{++}(t) - \tilde{Z}_{ij}^{++}(t)] - \lambda_{ij}^{-} F_{ij}^{++}(t)[\tilde{Z}_{ij}^{++}(t) - U_{ij}^{++}]^{+} - \omega_{ij}^{-}[\tilde{Z}_{ij}^{++}(t) - V_{ij}^{++}]^{+}, \tag{53}$$

subject to the constraint $0 \leq \tilde{Z}_{ij}^{++}(0) \leq Z_{ij}^{++}(0)$, where ω_{ij}^{+} is a positive constant and ω_{ij}^{-} is a non-negative constant. (52) is simply (28) with (51) replacing (31). The meaning of (53) is best understood by breaking up the right-hand side of (53) into three parts, namely

$$\dot{\tilde{Z}}_{ij}^{++}(t) = \tilde{A}_{ij}(t) + \tilde{B}_{ij}(t) + \tilde{C}_{ij}(t), \tag{54}$$

where

$$\tilde{A}_{ij}(t) = \omega_{ij}^{+}[Z_{ij}^{++}(t) - \tilde{Z}_{ij}^{++}(t)], \tag{55}$$

$$\tilde{B}_{ij}(t) = -\lambda_{ij}^{-} F_{ij}^{++}(t)[\tilde{Z}_{ij}^{++}(t) - U_{ij}^{++}]^{+}, \tag{56}$$

and

$$\tilde{C}_{ij}(t) = -\omega_{ij}^{+}[\tilde{Z}_{ij}^{++}(t) - V_{ij}^{++}]^{+}. \tag{57}$$

(54) and (55) represent the fact that transmitter is mobilized at a rate proportional to the amount $Z_{ij}^{++}(t) - \tilde{Z}_{ij}^{++}(t)$ of unmobilized transmitter. (54) and (56) show that an amount of mobilized transmitter equal to $\tilde{W}_{ij}^{++}(t)$ is released at time t. (54) and (57) represent the fact that mobilized transmitter has a tendency to become demobilized at a rate ω_{ij}^{-} until only an amount V_{ij}^{++} of transmitter is still mobilized.

We will now study the qualitative behavior of (52) and (53) in a special case of some interest. Let (36) hold once again, and choose the following values of the parameters of (52) and (53) for simplicity:

$$U_{ij}^{++} = V_{ij}^{++} = 0,$$

and

$$\lambda_{ij}^{+} = \omega_{ij}^{-}.$$

Since we are interested in the transient response of (52) and (53), the approximation $z_{ij}^{++}(t) \cong z_{ij}^{++}(0)$ is again admissible. We also introduce the following notation for convenience:

$$\begin{aligned} x(t) &= Z_{ij}^{++}(t), \\ y(t) &= \tilde{Z}_{ij}^{++}(t), \\ F &= F_{ij}^{++}(t), \\ a &= \lambda_{ij}^{+} = \omega_{ij}^{-}, \\ b &= \delta_{ij} z_{ij}^{++}(0), \\ c &= \lambda_{ij}^{-}, \\ d &= \omega_{ij}^{+}. \end{aligned}$$

Then (52) and (53) can be written in the form

$$\dot{x}(t) = a[b - x(t)] - cFy(t), \tag{58}$$

$$\dot{y}(t) = d[x(t) - y(t)] - cFy(t) - ay(t), \tag{59}$$

for $t \geq 0$, where $0 \leq y(0) \leq x(0)$. To fix ideas, suppose that no presynaptic spiking has occurred before time $t = 0$. Then (58) and (59) become

$$\dot{x}(t) = a[b - x(t)]$$

and

$$\dot{y}(t) = dx(t) - (a+d)y(t)$$

for $t < 0$. We can therefore suppose that

$$x(0) = b \tag{60}$$

and

$$y(0) = \frac{db}{a+d}. \tag{61}$$

We will show that $y(t)$, for $t \geq 0$, decays monotonically to a positive minimum for every fixed positive F. $cFy(t)$ therefore jumps from zero to a finite maximum at $t = 0$ and thereupon decreases monotonically to a positive minimum. In other words, the excitatory transient of Fig. 11 sets in, even if transmitter must be mobilized before it is released.

To prove our claim, let $w = x - y$. By (58) and (59),

$$\begin{aligned} \dot{w} &= \dot{x} - \dot{y} \\ &= a(b - x) - d(x - y) + ay \\ &= -(a+d)(x - y) + ab \\ &= -(a+d)w + ab, \end{aligned} \tag{62}$$

and

$$\dot{y} = -(a + cF)y + dw. \tag{63}$$

(62) can be integrated directly. We find using the initial data (60) and (61) that

$$w(t) = \frac{ab}{a+d}e^{-(a+d)t} + \frac{ab}{a+d}[1-e^{-(a+d)t}]. \tag{64}$$

$$= \frac{ab}{a+d}.$$

Since $w(t)$ is constant, the amount of mobilized transmitter is a fixed fraction of the total amount of transmitter. Substituting (64) into (63) allows us to integrate (63). We find that

$$y(t) = \frac{bd}{a+d}\left\{e^{-(a+cF)t} + \frac{a}{a+cF}[1-e^{-(a+cF)t}]\right\}. \tag{65}$$

By (65), $y(t)$ is a monotone decreasing function. $y(\infty) = \lim_{t\to\infty} y(t)$ exists and equals

$$y(\infty) = \frac{abd}{(a+d)(a+cF)}, \tag{66}$$

which is monotone decreasing in F. The amount of available transmitter released per unit time is

$$cFy(t) = \frac{bcdF}{a+d}\left\{e^{-(a+cF)t} + \frac{a}{a+cF}[1-e^{-(a+cF)t}]\right\},$$

which jumps from zero to a maximum of

$$\frac{bcdF}{a+d} = \frac{\delta_{ij} z_{ij}^{+\,+}(0)\lambda_{ij}^{-}\omega_{ij}^{+}F}{\omega_{ij}^{-}+\omega_{ij}^{+}}$$

at time zero, and thereupon decays to an asymptotic value of

$$cFy(\infty) = \frac{abcdF}{(a+d)(a+cF)}$$

$$\frac{\lambda_{ij}^{+}\delta_{ij} z_{ij}^{+\,+}(0)\lambda_{ij}^{-}\omega_{ij}^{+}F}{(\omega_{ij}^{-}+\omega_{ij}^{+})(\lambda_{ij}^{+}+\lambda_{ij}^{-}F)}.$$

$cFy(\infty)$ is a monotone increasing function of F.

Suppose, by contrast, that the rate of transmitter mobilization $\tilde{A}_{ij}(t)$ in (55) depends directly on spiking frequency, rather than being merely indirectly due to release of mobilized transmitter. For example, let

$$\tilde{A}_{ij}(t) = \omega_{ij}^{+}[Z_{ij}^{+\,+}(t) - \tilde{Z}_{ij}^{+\,+}(t)]F_{ij}^{+\,+}(t).$$

It can readily be shown that $y(t)$ rises from zero to a maximum and

then decays to a positive asymptote for $t \geq 0$. As a function of F, $y(\infty)$ first increases from zero to a maximum and then decreases to zero as $F \to \infty$, whereas $cFy(\infty)$ is a monotone increasing function of F which is quadratic in F at small values of F and saturates at a finite value as $F \to \infty$.

26. Concluding Remarks

The above-mentioned phenomena are all formal consequences of the psychological equations derived in Grossberg (1969*a*,*b*). We have changed the form of these equations in only one way. Namely, we have required that all processes occur at a finite rate. This requirement does not add any new psychological or neural postulates. The couplings whose rate we wish to make finite are already given by the psychological derivation, and these form the content of the theory. The fact that new transient features enter the equations when we slow down their interactions is no surprise, but it is gratifying that these transients seem to be found qualitatively in neural experiments.

The task of interpreting our equations and rendering all of their interaction rates finite is definitely not complete. Every appearance of an algebraic coupling in our equations is a candidate for our slowing down procedure, and every successful application of this procedure presumably contains more information concerning various rapidly varying aspects of neural interactions. We shall continue this procedure in another place.

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