the intact animals. In contrast, the oil-treated controls showed very high intromission/mount ratios both when intact and with testosterone replacement after castration. The possibility cannot be excluded that the failure of the estrogenized males to achieve normal numbers of intromissions is due to lack of development of the accessory sexual apparatus, particularly the os penis, as has been found by Beach in neonatally castrated males (*6*). If this is so, it will be necessary to identify the mechanism through which the neonatal estrogen injection can cause this block in development. The testes of the estrogenized males ($\bar{x}$=1.95 g) were significantly smaller ($p < .001$, 25 *df*) than those of the controls ($\bar{x}$=3.47 g). Previous research (*2*) has shown that the accessory sexual organs, such as the seminal vesicles, are also small and undeveloped in males given this dose of estrogen neonatally.

These data are difficult to reconcile at this time with the hypothesis previously proposed by Harris and Levine concerning the effect of neonatal hormones on the sexual differentiation of the central nervous system. The evidence thus far suggests that the newborn rat of either sex possesses a common, undifferentiated regulatory mechanism for the cyclic release of gonadotrophin from the anterior pituitary. During development in the neonatal female rat, this mechanism becomes fixed in its original cyclic pattern. During the critical period of the first few days of life in the neonatal male (*7*), this mechanism appears to be organized and changed to one of acyclic gonadotrophin release by the secretions of the infantile testes. If the newborn male is castrated or the normal secretion of the testes blocked in some other way, the original cyclic mechanism is retained throughout adult life. Conversely, if the neonatal female receives androgens during the critical period (*8*), the original cyclic mechanism is differentiated therefore into an acyclic pattern. Thus, the nature of the hypothesis implicates testosterone as the active hormone organizing the sexual control system, both in terms of reproductive cycles and sexual behavior.

Therefore, the effects of estrogen on the male may be accounted for by the direct action of large doses of estrogen on the neonatal testes (*9*), producing a male that is functionally partially castrated. However, the estrogenized males in this study actually showed a great deal of sexual vigor, although their orientation to the female in mounting was strikingly different from normal.

The more difficult finding to integrate with the hypothesis, however, is the action of estrogen in the neonatal female. If the main organizing hormone is that secreted by the neonatal testes, why does neonatal administration of estrogen produce effects that are in many ways similar to those produced by neonatal administration of testosterone? In the male, the effects of neonatal hormones seem to show some degree of specificity. Testosterone administered to the infant male rat in large doses produces little or no effect on sexual behavior and reproductive capacity (*2*). In contrast, the neonatal female rat shows a greater degree of nonspecificity to the action of the sex steroids. Whether other steroids will produce similar effects has not been determined as yet. Although these effects initially appear to be somewhat paradoxical, the influence of gonadal hormones administered in infancy upon adult patterns of both sexual behavior and gonadotrophin secretion appears now to be a well-established phenomenon.

SEYMOUR LEVINE
RICHARD MULLINS, JR.
Department of Psychiatry, Stanford University School of Medicine, Stanford, California

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Synaptic "Learning" Due to Electroosmosis: A Theory

Abstract. *Since the interstitial water of the central nervous system is in narrow channels between cells that have surface charge, electroosmotic flow of water should accompany current flow. Current density is high close to an excitatory postsynaptic membrane and the electroosmotic effect must be significant. Simultaneity relationships between action potentials in pre- and postsynaptic cells affect postsynaptic membrane current density and modulate the effect in a way which should produce "learning."*

When electric current flows in a liquid which is surrounded by a substance with a surface charge, the liquid will move. This is the phenomenon of electroosmosis. It can be shown that electroosmotic water flow is probably a powerful factor by which electrical activity can cause morphological change in the central nervous system. Furthermore, the effect is sensitive to whether or not pre- and postsynaptic cells fire simultaneously, and therefore will exert an integrative influence on synaptic relations.

A simplified basis of electroosmosis is described as follows. If the wall of a channel containing water has a negatively charged surface, the water will have an equal and opposite net positive charge. The layer of positive charge in the water is at the surface, and, for mammalian ionic strength, is about 10 Å thick. When an additional voltage is applied along the channel, the net positive charge on the surface of the water will move and carry water with it, as illustrated in Fig. 1. For negatively charged surfaces, the water will move in the same direction as electric current. There will be no pressure gradient with this water flow (*1, 2*).

At physiological *p*H and ionic concentrations, zeta potentials (a measure of surface charge) of −10 to −30 mv are uniformly obtained (*3*). While I am not aware of any studies having been made on neurons or neuroglia, it is reasonable to assume that these cells would be like all others. Therefore, a zeta potential of −15 mv will be assumed for the plasma membranes of neurons and neuroglia. (The surface charge is unrelated to transmembrane potential.)

It will also be assumed that the narrow space separating cells of the central nervous system is an aqueous phase. This assumption is almost uniformly made by neurophysiologists and is supported by recent evidence from electron microscopy (*4*).

A previous paper has given an analysis of many aspects of current flow in the central nervous system (*5*). Closer to a current source than one length constant of neuroglia, about 5 to 10 μ (*5, 6*), little current flows through cells and virtually all flows through interstitial space. The current flow around an excitatory synapse is as illustrated in Fig. 2.

The expression for electroosmotic flow in a cylindrical tube (*1, 2*) also holds for flow between two parallel walls. This formula is

$$v = (\text{grad } V)\ D\ \zeta/(1.13 \times 10^6\ \eta)$$

where v is the velocity of water flow in centimeters per second, ζ is the zeta potential of the cell wall in volts, D is the dielectric constant of water, grad V is the voltage gradient in the interstitial space in volts per centimeter, and η is the viscosity of the fluid in the interstitial space in poise. The factor of 1.13×10^6 converts to practical units. This formula gives only the steady-state value, but the relaxation time of the effect is short enough so that transients can be ignored (*1*, p. 109). An assumption used in the derivation of the formula that the width of the channel is much greater than the region of the net positive charge may not hold, but this introduces an error of less than a factor of two.

Grad V is equal to $-J \times R_o/p_o$, where J is the current density coming from a neuronal membrane source in amperes per square centimeter, R_o is the resistivity of the interstitial space in ohm centimeters, and p_o is the ratio of the total cross sectional area of interstitial space at a given distance from the synaptic membrane to the area of the synaptic membrane. The expression $1/p_o$ is a measure of the extent to which current density is increased due to the small interstitial space; p_o will increase with increasing distance from the synaptic membrane due to current divergence (Fig. 2). Let us solve for the case just outside the synaptic cleft, where p_o should be approximately equal to the proportion of total tissue which is interstitial space—about 0.05. Within the synaptic cleft, p_o will be many times less than this value. However, the case

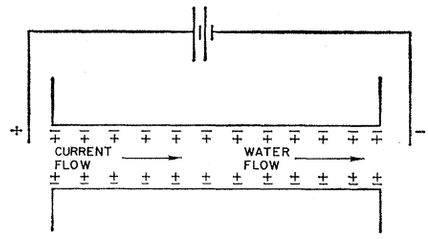

Fig. 1. Diagrammatic model of electroosmosis. The surface of the container has the fixed negative charges; the surface of the water has the positive charges, which are movable.

within the synaptic cleft will not be considered, as the membrane surfaces are specialized and may well be different from other cells.

Information is available about all of the terms in the formula with the exception of R_o and η. The values of both of these terms may well be higher between cells than in the bulk phase. However, factors which would increase the resistivity would also increase the viscosity of the interstitial space, and vice versa (*7*). Since the terms appear as a ratio, their values in bulk phase can be used to give an order of magnitude value.

Let $R_o = 60$ ohm cm, $\zeta = -15 \times 10^{-3}$ volt, $D = 74$, and $\eta = 6.8 \times 10^{-3}$ poise. Then $v = 0.17\ J$.

It is possible to make an order of magnitude estimation of the value of current density at a postsynaptic membrane. Araki and Terzuolo (*8*) found a peak synaptic current of 2×10^{-8} amp for a subthreshold excitatory postsynaptic potential (EPSP) of 6 mv in a motoneuron. Aitken and Bridger (*9*) show there are at least 16,000 synaptic boutons on an average-sized motoneuron of about 80,000 μ^2 (8×10^{-4} cm^2). Szentagothai (*10*), using a Nauta stain on a motoneuron after removing the dorsal roots, found five to ten degenerated synaptic endings. He estimated that he was staining about half of the degenerating endings. Assuming that 20 synaptic endings produce a 10-mv EPSP, the current density through the postsynaptic membrane at the excitatory synapse will be 3.3×10^{-2} amp/cm^2. This is not unreasonable, since at a neuromuscular junction it can be calculated from better data than is available for the motoneuron that a synaptic membrane current density of at least 3×10^{-2} occurs (*11*). Therefore, $v = 5.7 \times 10^{-3}$ cm/sec, or 570 Å/msec, which is about the duration of the peak synaptic current. The estimate of Szentagothai of the number of monosynaptic synaptic knobs may well be much too low, and therefore the estimate of synaptic current density may be too high by a factor of as much as 10. However, this would still produce a sizeable water flow.

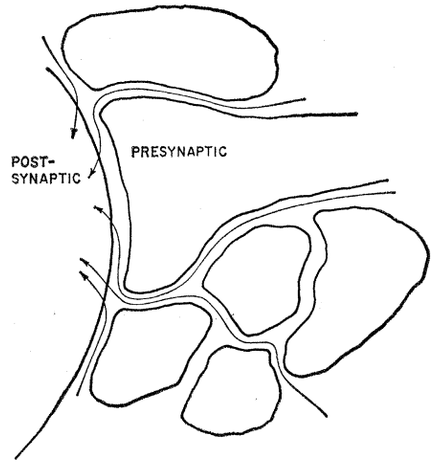

Fig. 2. Current flow around an excitatory synapse. The presynaptic and postsynaptic cells are labeled. The other cells are neuroglia. The fine lines with arrows are current flow. The separation between cells (interstitial space) has been drawn disproportionately large.

In general, the proportion of current carried across the synaptic membrane by negative ions will be different from the proportion carried in interstitial space. Therefore, current flow will cause a change in osmolarity, which in turn will affect water motion. Let us call this the osmotic effect. Although the magnitude of this osmotic effect cannot be determined from data presently available, the magnitude will be proportional to synaptic current, as is the electroosmotic effect. Possible implications of this will be discussed below.

The pressure required to stop the electroosmotic flow is called electroosmotic pressure (*1, 2*). By Smoluchowski's Eq. 24, the electroosmotic pressure in dynes/cm^3 is $1.42 \times 10^{10}\ J$. For $J = 3.3 \times 10^{-2}$ amp/cm^2 grad $P = 4.7 \times 10^8$ dyne/cm^3 or 35 mm-Hg/μ. This pressure gradient will decrease with increasing distance from the synaptic membrane as p_o increases. However, this gradient will be maintained for about 2 μ. Across this 2 μ there would be a pressure difference of 70 mm-Hg. (Since resistivity is not divided by viscosity in calculating this pressure, and the bulk phase value is used, the calculated pressure is a lower

limit.) With the possible exception of the osmotic effect, I can think of no way the central nervous system could develop anything like this pressure difference across 2 μ in 1 msec. The electroosmotic flow of water cannot be swamped out by other factors.

The flow of water in the interstitial space would not have an effect upon cells if it remained entirely interstitial. However, wherever current crosses a cell membrane, the membrane will appear as a source or sink of water flow relative to the interstitial space. A transmembrane electroosmotic effect in cell membranes has often been postulated (*12*). If this transmembrane electroosmosis were exactly equal to the effect in the interstitial space, there would be no net result; the water would move in a circle without generating any pressure. Since these two electroosmotic effects have a different physical basis, it is unreasonable to assume that the two would be equal. The synaptic membrane will be a source or sink of water and some pressure must be exerted on the membrane.

The example of an excitatory synapse was used intentionally, since excitatory and presumably inhibitory postsynaptic membranes have current densities higher by several orders of magnitude than any other parts of the central nervous system. During an action potential in a postsynaptic cell, the mean transmembrane voltage in the postsynaptic cell is about -10 mv. This potential is approximately the so-called "equilibrium potential" of an EPSP at which the excitatory postsynaptic membrane generates no current (*13*). Therefore, if a postsynaptic excitatory membrane is activated simultaneously with an action potential in the postsynaptic cell, much less current will flow across the postsynaptic membrane than was calculated for the subthreshold case above. Conversely, current density across a postsynaptic inhibitory membrane will be much larger if the postsynaptic cell *does* have an action potential simultaneously with activation of the postsynaptic inhibitory membrane, because the transmembrane potential will be further from the so-called "equilibrium potential" of the inhibitory postsynaptic membrane (*13*). (However, I know of no data from which to estimate the magnitude of inhibitory synaptic density.)

The mechanism can now be shown to perform an integrative function in the central nervous system. Let us coin the term "unsuccessful synaptic event" to refer to the following cases: (i) an excitatory postsynaptic membrane is activated and no action potential occurs in the postsynaptic cell, and (ii) an inhibitory postsynaptic membrane is activated and the postsynaptic cell *does* fire. Let us use the term "unsuccessful synapse" to refer to a synapse which usually has "unsuccessful synaptic events." The "success" of a particular synaptic event will then depend mostly upon the timing of the particular presynaptic input relative to other presynaptic inputs to the postsynaptic cell, that is, the central excitatory state of the postsynaptic cell at the time the particular presynaptic action potential arrives.

Since it takes many excitatory synapses firing closely together in time to fire a postsynaptic cell, the magnitude of the postsynaptic effect of any single synaptic event will have relatively little influence in determining its own "success." As shown above, the current flow and consequently the electroosmotic and osmotic effects are greatest with "unsuccessful" synaptic events. Even though there seems to be no way to predict just what these effects on synapses will be, the end result would be similar. For if the effect increases the efficacy of an "unsuccessful" synapse, it will tend to make the synapse more "successful," especially if the same thing is occurring simultaneously at other synapses on the same postsynaptic cell. If it decreases the efficacy of an "unsuccessful" synapse, it tends to destroy it as a synapse. So no matter what the effect, "unsuccessful" synapses will tend not to survive; they may either become "successful" or be eliminated as synapses. "Unsuccessful" synapses are unstable. "Successful" synapses are not affected, and are stable. Therefore, the proportion of the total synapses which are "successful" is maximized.

On psychological grounds Hebb and Milner (*14*) have proposed and developed the idea that learning might be due to synaptic efficacy increasing whenever a presynaptic excitatory fiber fires simultaneously with its postsynaptic cell. The electroosmotic effect and possibly the osmotic effect provide just such a mechanism, including a functional generalization to postsynaptic inhibitory synapses.

JAMES B. RANCK, JR.
Department of Physiology,
University of Michigan, Ann Arbor

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Albinism and Water Escape Performance in the Mouse

Abstract. *Observation of six inbred strains of mice in a water escape test revealed that albino strains perform markedly slower than non-albino strains. Performances of F_1, F_2, and backcross offspring of selected crosses between these strains indicated that there is an association between the homozygous condition for albinism* (cc) *and slow performance in the water escape test.*

This report presents evidence for an association between albinism and water escape performance in the mouse (*Mus musculus*). Albinism in the mouse is due to the homozygous recessive condition of the *c* allele at the *C*-locus in linkage group 1 (*1*).

Our measure of behavior (escape from water) is a quantitative character displaying continuous variation. It seems reasonable to assume that many loci are involved because behavioral characteristics are physiologically complex and undoubtedly are influenced by a variety of genes (*2*). However, such a character may be influenced by domi-