대한생리학회지 : 제1권 제1호 1967

Mechanical Physiology of the Somatic Nervous System

(Mechanical Transmission Mechanism and Initial Local Excitation of Somatic Neurons)

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=국문초록=

體性神經系의 機械的 生理學

(機械的傳達과 體性神經元의 初發局所興奮)

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郭　　在　　禧

人間의 感覺, 運動, 思考等에 直接關與하는 體性神經元이 人體內에 있어서 單一細胞動物과 非體性神經元과 같이 各種의 刺戟에 直接應하므로써 機能的 活動을 開始한다는 漠然한 豫想下에서 末梢에서는 或種의 痛素를, 中樞에서는 어떤 妙한 化學的인 興奮傳達物質을 探求하고 있으며 末梢의 痛興奮始發과 大腦皮質의 機能發生 같은 重要한 諸機轉이 解明될 可能性 조차 보이지 않는 것이 體性神經生理學의 現狀이다.

著者는 生態分離한 單一神經纖維實驗과 臨床的硏究로서 人體內의 體性神經纖維와 그 求心性終末은 最終 共通機械的刺戟을 받는 點을 立證하고 腦皮質內의 入射에 依한 Synapse 傳達이 機械的인 點과 毛細血管擴大에 依한 Glial Satellite 部의 機械的傳達과 Spine Koph 에서는 入射 없이도 Massage 에 依하여 初發脫分極이 發生될 必然性을 指摘하는 同時에 著者가 부르는 「體性神經系의 機械的生理學」에 依하면 難問에 屬하는 大多數의 神經現象과 精神現象이 具體的이며 合理的이요 또 實用的으로 解明됨을 實例를 들어서 例示한다.

本硏究는 拾數萬例의 單一神經纖維觀察과 數百例의 臨床的硏究와 最近高度로 發達된 技術에 依한 微少生理學的 諸硏究業績과 電子顯微鏡的形態學成果를 綜合하므로써 成立된 것이요 何等의 無理한 憶測을 內包하지 않음을 確信한다.

I. Introduction

"Neuron" as it is used here means the excitatory somatic neuron. In the somatic nervous system are included all those parts of the central and peripheral nervous system that convey impulses from the sense organs, organize them in the brain, and deliver motor impulses to the striated skeletal musculature of the body and limbs. Receptor-like neurons such as visual and olfactory cells are considered as a receptor cell than a neuron, and following neurons are naturally excluded; inhibitory neuron, secretory neuron, the central diffuse nervous system and the autonomic nervous system. We prefer to depend on the adequacy of a free use of language to establish satisfactory communication. We should not be coerced into greater precision of language.

That the brain is the bodily organ of the mind we have to accept as an established fact. Mind, meaning by that thoughts, memories, thinking, reasoning, sensing, voluntarily moving, and so on, is closely associated with the activity of the somatic neurons of the cerebral cortex. It is approximately correct to say that somatic neurons do not fire without stimulations, though some cortical neurons show spontaneous small action potentials appearing at irregular intervals. We know that somatic neurons defy both electrical transmission and acetylcholine transmission, but we do not know much about their lucid transmission mechanism at the periphery and in the cerebral cortex.

When we go to the explanations of mental events, we find many views consonant with the thought of power as the physicist uses the word; mind, psychic tension, consciousness, sensory intensity, mental energy, cortical energy, and many others of this sort are all alike in that they are capable of becoming weak or strong. They suffer, however, from lack of objectivity, and because of this they are still far from being a physical power inspite of so many physiological and psychological evidences.

It is very easy to adjust this sort of view to the neurophysiological notion of the central excitatory state. It thus appears that the shortest way to make psychology objective and to make neurophysiology to prosper maximally is not to ignore mental energy but to embody the central excitatory state with some concrete fact.

G. Kato and his collaborators reported about the physiological nature of an isolated afferent nerve fiber of warm-blooded animal (1), and demonstrated the isolation of a motor nerve fiber of cold-blooded animal (2) at the 15th international physiological congress. I was one of the collaborators. I reported an another experimental and clinical study which suggests mechano-receptor specificity of the somatic nerve (3) at the 23rd international congress of physiological sciences.

I have made a more straightforward attack on the precise nature of the central excitatory state, and noticed that the simple fact of mechanical transmission is of vital significance for the initiation of the local activity of somatic neurons in human body and it certainly seems to constitute a sufficient answer to the difficult question about the nature of the central excitatory state.

Most neurophysiologists do not wish to spend their energies in a study of this short of physiology. If a problem is not already bathed in the bright lights of a developed research method, they avoid it, seeking that which is more easily seen. Fashions obtain here as they do elsewhere. However, if something is not absolutely impossible, and if we want it badly enough, we will achieve it, sooner or later. I beg the reader's patience till he has read through this paper. This study was orally delivered as a special lecture at the 18th meeting of Korean Physiological Society held in 1966.

II. An Experimental and Clinical Study About Living Nerve Fiber And its Endings

I have made a clear and simple observation as in the following employing over thirty years time.

1. An isolated single nerve fiber gastrocnemius preparation of the toad was laid in a shallow pool of Ringer's solution on a glass plate. Purulent matters of various sorts, emulsions of morbid tissues, hot Ringer's solution, alcohol, hydrochloric acid, liquid ammonia, mustard and acetylcholine were not an effective stimulus to the axon when applied to the single fiber on the Ranvier's node.

2. It was almost impossible to cut a motor nerve fiber with a needle or blade without eliciting nerve impulses.

3. Nerve impulses did not appear when single nerve fiber sartorius preparation of toad was put into Ringer's solution contained in a glass cylinder having a hydrostatic pressure of 30 kilograms through the use of a piston.

4. N. ulnaris was effectively stimulated by striking at the elbow just two thousand times in a duration of ten hours without resulting in any paralysis of the fingers. The slight and transient movement of the little finger and ringfinger resulting each time indicated that the motor nerve fibers are stimulated without being damaged.

5. In cases of an abscess in the deeper layer of the skin or of a large pustule under the horny layer of the sole, the pain was immediately relie-

ved by removal of the content by aspiration, but when novocaine solution was injected rapidly into the site, the pain increased in proportional with the rising pressure.

6. The spontaneous burning pain of causalgia was apparently reduced when the contracted mummy-like skin was softened by moisture. The pain was gradually removed when capillary blood flow was increased by periarterial sympathectomy.

7. In the case of a dry brand patient, histologic study revealed that the epidermic cell atrophy and the narrowing of the intercellular spaces are distinct in the painful atrophic area from the pain free skin enclosing the painful region.

8. While alcohol, weak hydrochloric acid, liquid ammonia and mustard gave a severe pain when applied to a purposefully made cut wound on the palm, acetylcholine did not cause any pain.

The above results mean by implication that somatic neurons in human body have mechanoreceptor specificity as the truth behind their functional activity. An implication is often more important than to look the facts in the face. After much thought about the matter, I became aware of that it is most reasonable and also practicable to set forth the thought of mechanical physiology of the somatic nervous system.

Mechanical transmission mechanism is not a new. Unfortunately, however, it is not taken seriously, and most somatic nervous and mental phenomena still remain vaguely understood for some reason, not explained. That even the peripheral pain producing mechanism is not yet satisfactorily understood is deplorable.

III. Mechanical Transmission at the Periphery

Within the individual neuron, graded response mechanisms have been identified at either end of the classically conducting nerve fiber. They have no true refractory period and they support local activity at a stimulated region without propagating of impulses.

The skin can everywhere be stimulated by light pressure to give the sensory response called pressure. When an object is touched, the external displacement of the hair transmits a motion along its length and stretches and compresses the tiny terminations of the neuron that are wrapped around the base of the hair follicle. The initial depolarization of these nerve endings is produced by such mechanical distorsion. The mechanical distorsion of the nerve endings of a Meissner corpuscle is conveyed through the displacement of the surrounding skin tissue. An increase in the forces that normally bear on the outer skin causes the successive concentric layers of a Pacinian corpuscle to slide on one another; this squeezes and twists the internal nerve endings in such a way to depolarize the membrane mechanically. No one doubts that natural mechanical stimulus causes depolarization of the sensory nerve endings in the muscle spindle and of the Golgi tendon organ and a local potentials which spreads electrotonically along the axon. This local potential gives rise to repetitive discharge in the sensory nerve.

All this clearly shows that mechanical switching mechanism is actually going on in our body. Chemical transmission or electrical transmission hardly needs to be considered in these cases. Adequate mechanical stimulation, meaning by that mechanical stimulation of a nerve without damage, is a wise provision of nature. Artificial mechanical stimulation of an isolated single nerve fiber with needle or hair always produces nerve impulse, but injury of the fiber is in general unavoidable. Contrary to this, nerve fibers in the nervus ulnaris can be stimulated repeatedly by external mechanical stimuli without being destroyed. From these it is easy to understand that somatic nerve fiber and ist endings in the body are nicely protected as to receive adequate mechanical immediate stimulus that is not too strong and not too weak than that of the order of magnitude of the energy required to trip the switch for the permeability increase in membrane local excitation.

It will thus be seen that in the laboratory the electric current is the most general stimulus for provoking activity of nerve, but in the human body mechanical immediate stimulus is the most adequate form of energy for initiating activity of the somatic nerve and its endings. The events in excitation and in conduction are separate problems.

In unicellular organisms, reception and conduction and response take place in the same cell. Complex animals have specialized structures, sensitive to different kinds of stimuli, which are known as receptors. Some say that the function of receptors is to convert various kinds of stimulus energies, and the excited receptors act as a new stimulus to their nerve terminations. There is as yet no evidence which shows that afferent nerve endings are employing any other form of energy than the mechanical as their immediate natural initial stimulus. From these it seems that there is no room to suspect the conclusion that the transmission from receptors to their nerve terminations is mechanical.

Evidences suggest that the microphonic potential originates from a non-neural structure. Some workers believe that cochlear microphonics are the normal stimulus of the acoustic nerve endings, but there is no definite proof that this is so. The cochlea as a whole is a device whereby sound waves are translated into nerve impulses. We may safely say that the nerve endings receive mechanical stimulus by deformation of the hair cells.

The taste receptors are stimulated by chemical stimuli. The nature of the transmission between the taste receptors and innervated sensory nerve endings remained obscure, but now we can confidently expect that all sensory nerve endings have the same physiological attitude in marked contrast to various receptor cells.

The aortic and carotid bodies are sensitive to variations in the partial pressure of O_2 and CO_2 and in hydrogen ion concentration, and to certain drugs. Stimulation of these receptors provokes the discharge of impulses along the sensory nerves, but this does not mean that transmission between receptor cells and nerve endings is chemical. O_2 and CO_2 and hydrogen ion in solution are unable to stimulate nerve fiber and its endings humorally. They cause depolarization of the nerve endings indirectly by producing deformation of receptor cells. A degranulation of the epithelioid cells, contained in the carotid bodies, is found when the oxygen tension was reduced to lethal levels (4). This indicates some mechanical changes of the epithelioid cells.

The widespread view that the biological function of the elaborate sense organ is to lower the threshold of the nerve fiber to some form of energy is in error in supposing that the nerve fiber is sensitive to stimuli of various kinds and all the properties of a nerve lie in the nerve itself. It is very doubtful, or wholly impossible, that specialized nerve endings exist in much of the body surface. Every one knows that nerves of low threshold are quiescent without stimulation and that of high threshold are able to produce impulses by a stimulus of sufficient strength. The point is their stimulus and not their threshold. There is no doubt that afferent nerve ending and receptor cell take their own attitude toward stimuli. In view of functional and structural evidences, it seems rather natural to conclude that each type of sensory receptor is especially sensitive to one form of energy and the receptors analyze the complex energy pattern of the external world and translate the complex impression into an intricate pattern of mechanical stimuli which are responsible for the initial depolarization of nerve endings. Without making this point clear, we are unable, it seems, to expect a really and truly scientific and practicable physiology of somatic nervous system. We may say that we are in a position to postulate mechanical physiology of the somatic nervous system.

IV. Peripherial Pain Producing Mechanism

Pain is important in survival and longevity. Useful symptomatic pain warns of disease which can be treated. It does not seem peculiar or startling to conclude that sensory nerve endings directly related to various receptors are not essentially different from the free nerve endings in their physiological property when we remember that there is no anatomical evidence for differentiation, for the free nerve endings and other nerve endings all look alike.

Free nerve endings are not a receptor but a mere nerve ending, and surrounding tissues are indeed intended to detect various noxious stimuli because of nonspecialization. There is no reason to say that the free nerve endings are specially endowed as to react to extreme degrees of various kinds of stimulation. When the tissues are confronted with various noxious stimuli, the free nerve endings immediately receive an apt mechanical stimulus from the tissue cells themselves without being damaged.

The answer to the question as to how pain endings select all intense cutaneous stimulations is plain; they display mechano-receptor specificity, and, since they are immersed in tissue fluid, they receive adequate mechanical stimuli only when surrounding tissues are deformed by potential stimuli and thus become to exert mechanical action upon the pain endings. It is clearly a fundamental error to suppose that all the properties of a nerve lie in the nerve itself.

Ebbecke proposed that something is released by stimulated cells, which causes vasodilation and pain (5). Lewis called it histamine-like substance (6). There is, however, no need to speculate some subtle chemical substances which are released from damaged cells and produce pain impulses by humoral action.

Pain fibers discharge spontaneously when the tonus of an acute inflammatory locus reaches a certain degree by cell swelling, cell infiltration, and capillary dilatation. Finger press upon an abscess or novocaine injection into the abscess cavity increases pain, while a small incision relieves the patient from the pain We know that tension is a frequent cause of pain; e. g., when a hair is pulled the pain is due to tension exerted on the nerve endings, pulsating pain is produced by distension of the tissues, more solidly packed by pathologic changes, at each systolic wave, and the immediate relief felt on opening an abscess is due to release of tension. Some chemical substances produced in the inflammed region might be considered effective, but this does not explain the rapid alleviation of the pain after an incision of the abscess. Hardly believable is such a rapid dilution of the imaginary pain substances. There can be no objection to the conclusion that pain endings in this case are stimulated by internal adequate mechanical stimuli. When considered in the light of mechano-receptor specificity of somatic neurons in natural environments, the experimental fact that isolated single nerve fiber is not sensitive to various kinds of venomous purulent matters becomes a matter of course.

Damage to the skin that diminishes the thickness of the epidermis, sunburns, inflammatory process, etc., lower the pain threshold of the skin. We have no reason, however, to say that the threshold of the very free nerve endings is lowered. In the case of inflammation, the threshold of the nerve endings must be hightened by the increased acidity of regional tissue fluid.

The intact skin is not sensitive to alcohol, but if the horny layer of the skin is removed the epidermic cells are made accessible and a smarting sensation is produced by immediate mechanical stimulation of the nerve endings. The explanation that nerve endings are stimulated by alcohol is erroneous. Single nerve fiber can never be stimulated by alcohol. Nerve endings must be the same.

When the cornical point of a needle penetrated into the skin, some of the very numerous free nerve endings may probably be damaged. As already known by the experiment with isolated single nerve fiber preparation, damaged nerve fiber does not produce repetitive excitations. Free nerve endings must be the same in this point. The tension within the skin must increase by the needle prick, but increased hydrostatic pressure can not stimulate the nerve endings if they were immersed in tissue fluid. All this shows that the sustained pain after needle prick is not due to the damaged nerve endings but to the repetitive local excitations of the nerve endings that are stimulated by adequate mechanical stimuli resulted from epidermic cell deformation. The pain will continue after removal of the needle while the internal mechanical stimuli are maintained The important point is that the adequate mechanical stimulus is ordinary routine of initial activation in the body.

Causalgia is commonly accompanied by local anemia and atrophy resembling to spontaneous gangrene, which may naturally cause a decrease in lymph and consequent narrowing of the intercellular space of the epidermis in which pain endings are distributed. Thus the surrounding tissues will press the endings when solid contact is produced and be so changed so as to conduct mechanical force more easily to the pain endings. The very contrary is the case of the pain endings in the edematous skin. The pain endings in both the causalgic skin and edematous skin must be pretty much alike, nevertheless the senses of the edematous skin grow dull because of high threshold of the skin. The distinction between the threshold of the skin and that of the nerve ending must be rigidly maintained. The theory that efferent sympathetic tonic impulses, continuously flowing out to the peripheral blood vessels, join up directly to the afferent pain fibers so that there is a constant pain related to the tonic sympathetic innervation of the peripheral area is untenable. Such junction has never been demonstrated.

Cessation of peripheral pain requires only that the strength of that mechanical adequate stimulus be diminished below the critical threshold level. On the basis of internal natural adequate mechanical stimulus, we can give a very cogent reason for almost all the clinical and non-professional treatments for soothing pain, such as massage, hydrotherapy, thermotherapy, sympathectomy, fever anesthetics and many others, excepting anesthetization and operative severance of the pain afferents.

The fact that almost all the peripheral pain producing and soothing mechanisms can be uniformly explained by the state of the mechanical immediate stimulation of the pain endings must deserve a due consideration. Experimental data are important when they are significant, when they yield the broadest generalization or most numerous relationships.

The ancients were aware of the effects produced when mechanical forces act upon the solid bodies, and used such simple machine as the lever. Wind power can turn windmills. A water wheel is pushed by moving water. The energy of fuel is transformed into mechanical energy when gasoline and oil are fed into an internal-combution engine and when coal fires a steam engine. In the case of the mechanical relation of the nerve endings and directly related tissues, common sense must be used as usual, and that will do fully.

It needs no great erudiation to tell that the piano is quiescent unless the pianist plays it. Functional or induced firing of the somatic neurons in the body is going on in the same way. With but a hazy understanding of the “switcher” we can hardly expect a more sound and efficient physiology about pain phenomena and cerebrocortical processes. At all events the research after the switcher is the first thing the neurophysiologist must do We are now talking about it. The hypothesis of some unknown chemical transmitter hardly needs to be considered in the cases of peripheral pain producing mechanism and cerebro-cortical mechanism. It is highly desirable to reconsider whether the influences of the chemical transmission theory produce progress or cause hindrance in the physiology of the somatic nervous system which is the most important organ of human mind and human behavior.

V. Synaptic Mechanical Transmission

The horizons of microscopy have been greatly expanded extending our knowledge of the structural organization of protoplasm down to the level of macromolecules. Differentiations can be considered as derivations of specific adaptations or modifications of some of the main cellular components, such as the plasma membrane or the devices of cell attachment.

The tight junction, the intermediate junction, and the desmosome (macula adherens) of epithelia are the specialized sites of firmer attachment between epithelial cell surfaces. Desmosomes vary somewhat in their structure in different tissues. In the synapse of central nervous system, the desmosome consists of two dense plaques on the opposing membrane surface, separated by an intercellular space about 200 Å wide. The contents of the intercellular space of the desmosome is somewhat dense than that of the intercellular space elsewhere and some desmosome shows a slender more dense intermediate line. The modifying term "adherens" implies a solid contact. It is clear from the relative toil with which synaptic knobs are separated from the post synaptic membrane during specimen preparation that the electron dense structures of attachment endow the whole specialized border with a considerable degree of rigidity.

Synaptic structures in the central nervous system are actually complex. The synaptic cleft in most cortical synapses is larger than the spaces between other membranes and shows a system of fine intersynaptic filaments of about 50 Å that join both synaptic membranes, separated by an intercellular space about 300 Å wide (7). The demonstration of intersynaptic filaments in between the membranes confirms that there is greater adhesion at the junction. In fact, in an isolated cell the synaptic endings break the connection with the axon, but remain attached to the cell.

Electron microscopic studies demonstrated that the plasma membrane forms small vesicles. Of great physiological and biochemical interest was the demonstration of the synaptic vesicles at the synaptic endings. In general terms in neural synapses a localized process of neurosecretion takes place, which is similar to the production of other neurohumors.

The synaptic vesicles have a diameter of 300 to 600 Å and a limiting membrane of 40-50 Å. They are distributed throughout the ending but tend to collect and to make close contact with the presynaptic membrane at certain points which show the device of attachment. That the vesicles are the storage sites of acetylcholine and other substances has also been proved by isolation of the synaptic vesicles. Recent study revealed that some synaptic vesicles attach to the presynaptic membrane opening into the synaptic cleft. There is no doubt that they flow and penetrate the presynaptic membrane, discharging their contents in the intercellular space.

As shown in the case of motor endplate, some of the vesicles of synaptic knob ought somehow or other to release their contents by inputs. Because of the mechanical power resulting from contraction of vesicles it is inevitable that the synaptic knob pulls the trigger or throws the switch and there results permeability increase of the post synaptic membrane as an effect. Connecting filaments of the cerebro-cortical synapse correspond closely with that trigger. The utilized power is only of the order of magnitude of the energy required to trip the switch and is therefore to be much less than that obtained from contraction of the large vesicles. From these simple reasons it becomes possible to understand synaptic transmission mechanism of somatic neurons as a cause-and-effect relation. This sort of adaptive device for the utilization of mechanical power is a wise provision of nature and we find it everywhere in the body but hardly be imitated. With respect to somatic neurons that are insensitive to acetylcholine and defy electrical transmission there is no need to speculate about some peculiar chemical transmitter. It is widely believed that the existence of vesicles is the proof of chemical transmission. Such conclusion is, however, obviously premature. If the effector is mechanophil, the transmission must be mechanical, and in fact the plasma membrane of the somatic neuron is very sensitive to mechanical stimuli.

The immediate stimulus cannot be fixed definitely, but must be chosen in accordance with the convenience of the effector. As is clear the events in excitation are another problem. It is idle to speculate as to which is more important, the chemical transmission or the electrical or the mechanical; and it is folly to bet one's fortune on the electrochemical transmission forgetting the mechanical transmission in so far as somatic neurons are concerned.

The reaction of the effect upon the cause matches the action of the cause upon the effect. Everything is interrelated in this way. Fundamentally, of course, the stimulus-response relation in biology is the relation of cause and effect, but the response is in general brought about by the combined action of several factors, and we are still unable to recover for practical use the convenient relation of cause and effect because the actual stimulus-response relation is tremendousely complicated. If we confine our attention to a single excitatory synaptic knob on cerebro-cortical neurons, where observation is more immediate and the temptation for insecure speculation is less, the mechanical work of the knob performed through connecting filaments (cause) has to match the permeability increase of the postsynaptic membrane (effect).

Morphological peculiarity of the dendritic spine of cortical neuron, electron microscopic speciality of its synaptic attachment comprising wider cleft, greater surface and filamentous adhesion, and rich supply of vascularity of the cortex forced us to the concluion that the head of the spine twists by the massage of neuroglial tissues and blood capillaries, and thus receives mechanical stimuli without any input. Cortical activation in this way is considered to be one of the mechanisms responsible for the restless firing of the cortex during waking state. The experimental fact that the dendrite of a neuron in tissue culture has greater susceptibility to mechanical injury than the soma (8) is strongly in favor of this mechanism.

VI. Mechanical Transmission at the Neuroglial Satellite in the Cerebral Cortex

It is widely believed that some cohesive force is operative over the entire surface of cell-to-cell contact. To what extent this cohesion is due to the intercellular material and to long range forces attributable to the property of the membranes themselves are not known.

Cerebral cortex is almost solidly packed with cellular elements, and microscopic study shows that some glial satellite cell adhears to burrow into the soma or the dendron, forming a small pocket for itself, and that in some cases there is glial intervention of only a few microns in thickness between neuronal membrane and capillary wall. In the interstices between the neurons there are, in fact, packed many glial cells and so many capillaries especially in the cortex. Glial satellite cells are particularly numerous around the small cells of the cortex. It is confirmed that the number of glial satellite cells of the anterior horn cells in the lumbar region increases by increased physiological activity (9). As is well known, satellitosis is an increase in the number of oligodendroglia neighborring a nerve cell body and is seen in certain toxic states. It is also known that cultured neuroglia cells show contraction-expansion movement, sticky process, active pinocytosis and migration to a relatively anaerobic area (10) (11).

The pattern of flow of the capillary bed constantly changes. Even though the small vessels depend upon the nervous controls of the large vessels for the shifting of blood from one organ to another as it needed, the control of the microcirculation in the cerebral cortex is largely independent of the rest circulatory system. The muscle cells of the arterioles and the capillary bed are, in fact, extraordinarily sensitive to chemical stimuli. It is well known that a wide variety of substances extracted from tissues and carbon dioxide and acetylcholine cause the small vessels to dilate. Whereas the muscle cells of the large vessels are isolated from the surrounding tissues in the thick walls of the vessels, the muscle cells of the thoroughfare gang and arterioles are immersed in the environment of the very tissues which they supply with blood. The contraction and relaxation of the muscle cells in the microcirculation of the cerebral cortex are thus under the joint control of chemical messengers in the blood, produced of tissue metabolism, and special substances liberated from axon endings.

Since capillary dilatation can attain a range of tens microns in diameter, the glial satellite, situated within the range of the operation of the mechanical power due to capillary dilatation, has to inevitably depolarize neuronal membrane mechanically when cortical capillaries dilate rapidly and push glial satellites against the neuronal membrane. There is no doubt that carbon dioxide, locally increased in the cortex during arousal, and acetylcholine, liberated from the axon endings during arousal, are of great importance for the vasodilatation.

Ingvar found that stimulating the reticular activating system in a neuronally isolated part of cortex, with pial circulation intact, produces electroencephalogram activation (12). He also reported experimental evidences which indicate that cortical blood flow increases when reticular activation is induced, and that the brain itself in arousal produces a humoral agent which gives rise to a small but definite increase of the blood pressure (13). The evidence from experiment with isolated cortex during arousal in the surrounding intact cortex furnishes irrefragable proof that synaptic transmission is not an absolute necessity for the activation of cortical neurons and a vascular phase is, in fact, used instead of synaptic activation in the reticular activation process. The evidence of a vascular phase in the activation process clearly indicates an indispensable extrasynaptic stimulation of neurons, and this vascular stimulation can be substantiated by the non-synaptic mechanical stimulation. From this, it is easy to understand why glial satellite cells are particularly numerous around the small neurons of the cortex.

That the function of products of tissue metabolism and neurohumoral substances formed or liberated by the nerve impulses is an important one is evidenced by several facts, but whether they are involved directly in the transmission of cerebro-cortical neurons was a highly controversial question. It now seems verified that they can involve through their action upon capillaries.

Neuroglia cells are commonly believed to provide mechanical and metabolic support for the neurons. Recently, interest has been revived in the possibility that the neuroglia cells of the cerebral cortex may play some important role for cerebro-cortical activity (14), but what fact concerning neuroglia cells has to do with cortical neuron activity remained to be demonstrated. Since neuroglia cells are very movable and also adhesive, one cannot doubt the rearrangement of neuroglial satellite cells during cortical activity.

The mechano-receptor properties of natural (15) and cultured (8) neurons are directly confirmed by using micro-electrodes.

These facts are ample for the concrete data concerning the proposition that mechanical transmission to the membrane, even outside of the synaptic area, is inevitable when adjacent capillaries are in full dilation. For the full understanding of nervous and mental phenomena, it was said that although there is available no direct experimental evidence to show that the central nervous system employs any other form of conduction of exciattion than the nerve impulses, it is only reasonable to view the possibilitty with an open mind. We now see that this has been proved valid by the undeniable mechanical transmission from the neuroglial satellite cell to the cerebro-cortical neuron.

It is now quite understantable that the stereotyped synaptic mechanical transmission and the elusive non-synaptic mechanical transmission are combining to afford the cortex a great capacity for activity, certainly in the cortex and perhaps in other parts of the central nervous system. What is fairly clear is that a somatic neuron is merely to react to stimulus and the everchanging intricate patterns of mechanical stimuli in the cortex are responsible for the great capacity of the cortex for activity.

It seems wonderful that the plastic and developmental nervous phenomena and the stereotyped synaptic phenomena can readily be explained objectively and also uniformly by mechanical inner stimuli.

VII. Mechanical Tension in the Cerebral Cortex

The question about mental power has engaged the minds of all times and all nations. The tension between the ideal and the real may be resolved in many ways in a healthy society; but it can never be taken as nonexistent. It is radically a question of biology. Psychological events constitute dynamic wholes, and all mental events belong in the cerebral cortex where they are finally determined.

The dynamic nature of cerebro-cortical processes and of mental processes generally indicates the existence of an implicit belief that the brain ought somehow or other to collect all sorts of influences in order to get some single unitary state that corresponds to what central excitatory state or cortical energy itself seems to be. The human mind is indeed both the object and the subject of psychologists' work, and our scientists lean towards accepting mind itself as a form of energy. There exists today a great deal of good physiological facts whose correlation with psychological events is well established.

As neurophysiology is prepared to render a systematic service to psychology, the science of mind, a physiological theory of neural action ought not seriously to be maintained if it is incompatible with psychological fact. If psychology is coordinate with physics and if the scientific method is applicable to both, then it seems strange that psychology has come such a little way when physics has ramified many fields and has come so far. From this it can be easily shown that there must be some gross fault in present-day neurophysiology.

There are no phenomena absolutely given; everything is a relation. It is well said that the central nervous system is a relational organ. The view of relational physiology will work as a real science only if the contents of that dynamic agent are certified as a concrete entity. What is wanted and wanting still is some reasonable conception of mind-body relation. As is often said, for the scientist there should be no doubt that the problem of interaction of mind and matter is a real problem and not a pseudoproblem arising from confusion in the usage of words. There is no reason to be fearful of scientific deduction about mental energy only in the sense of a real energy.

The older neurological literature is filled with references to nervous energy as the psychology is with mental energy. The doctorines of nervous energy, as derived by analogy with forms of physical energy, are in general opposed to theories of localization. They fit better the facts of plasticity of nervous function, but are of little help for an understanding of specific integration. Reflex theories are more adequate to the latter but are unsuitable to the mechanism of the less stereotyped forms of the cortex. The synaptic pattern is fixed, but the functional pattern plays over it without limitation to localized specific structure. That the higher level integrations are quite beyond the physiology of synapses and are a function of some more general, dynamic forces is clearly demonstrated by the experimental fact that stimulating the reticular activating system in a neuronally isolated part of cortex, with pial circulation intact, produces cortical activation by a simple vascular phase. Chemical pool theory and electrical field concept (16) proved of little use.

There is as yet no clue to the nature of the dynamic forces in nervous activity, but the obvious functional plasticity of the cortex compels the assumption of such physical forces as comparable to mental energy as before. In this impasse, it is of a fresh interest to demonstrate synaptic fixed and non-synaptic variable mechanical transmission mechanisms.

Neurophysiology started with such high hopes that all that was needed was the willingness to solve in terms of matter-energy system, but there has not been any great discovery that has revitalized the science-for a science it is-establishing neurophysiology as an eminently practicable science and removing hidden doubts. For the scientists fact and inexorable logic are the goal that is never forgotten. This cannot be too strongly borne in mind if neurophysiology is to prosper maximally. The present situation of the physiology of the somatic nervous system is, however, disappointing. A great majority of the physiologists hold chemical transmission theory, but they can not say more than some unknown chemical transmitter when somatic neurons are concerned. They are also quite uncritical of other kind of transmission than the electro-chemical. In studying the works of cerebral cortex, attack must be launched on many fronts. We catch more fish in the pond with the more fish in it.

Mechanical and thermal changes must also occur at the synapse. As surely everyone now knows, mechanical stimulus is a universal one, and mechano-receptor property of somatic neurons is directly proved. Furthermore, electron microscopic structures of synapses in cerebral cortex clearly shows the mode and place of a mechanical stimulation. Analysis is a necessary tool, and actual total events can be best understood as parts in relation. It is for this reason and for this reason alone that the subject matter of investigation in our "mechanical neurophysiology" is fixed to the natural mechanical switching mechanism where there can be no dispute about terms.

Some cortical neurons show random spontaneous small action potentials. There are also neurons which do not show any spontaneous activity. This small action potential is caelld "spontaneous" because its origin is not known. Under each end knob and neuroglial satellite cell there occurs local depolarization which is antecedent to evoked small action potential, but a sufficient area of the neuron membrane must be activated before a self-propagated large voltage impulse (evoked potential) is initiated. These spontaneous and evoked small action potentials actually summate and a potential can be built up which reaches the threshold and fires off a spike potential.

The occasional random firing of a few neurons cannot produce a conspicuous result. The evoked small action potentials, of course, present spatial summation and temporal summation. Since the depolarization at the neuroglial satellite is due to capillary dilatation, cortical mechanical tension resulted from increased blood flow of cortical capillaries is of vital importance for cortical activity.

During functional activity of any tissue, a large amount of blood is required which is supplied by arteriolar dilatation. The reticular formation has a significant role in determining our behavior and state of consciousness. Yet the final question, the search for the integral, is not yet answered. A single axon of reticular origin may produce a surprising variety of patterns. Its terminal neuronal process seems to refuse to stay explained in terms of the stereotyped synaptic neuronal circuit theory. It remains still obscure whether non-synaptic, reticulo-cortical terminations are of synaptic type or not. But it is certain that the reticular activating system can produce cortical activation through a simple vascular phase without any synaptic connection. In the cerebral cortex, not all knobs are synaptic. There are actually numerous knobs which do not make typical synapse in the cortex. It is highly likely that such non-synaptic knobs and non-specific reticulo-cortical terminations work as a vaso-dilator.

There are many drugs which dilate cerebro-cortical vessels, but there are very few agents known which constrict cerebro-cortical vessels. Adrenalin injection into the general blood circulation is followed by vasodilatation, because of a passive effect due to the rise in general blood pressure. The cerebro-cortical vessels are held in a state of tonic dilatation rather than in one of tonic constriction, as prevails in the vascular system of the rest of the body. These facts carry implications for the importance of maintenance of cortical mechanical tension.

There is probably little hope that the physiology of the higher mental processes will ultimately be worked up with the parsimonious conventional notions of neuron reflex arcs and humoral transmission. Contrary to this, so many lucid evidences force us to the inevitable conclusion that in both the periphery and the cerebral cortex, every event is transformed into the form of mechanical stimulus whether it be aroused by external stimuli or by internal processes, presenting the mechanical switching mechanism of the somatic neurons. That the cerebral cortex is in a state of physiological inflammation is an apt expression in an admirably lucid style when viewed from the mechanical relationship between cellular elements. The solidly adhibited tissues would produce the same mechanical stimulus to the neurons in the waking cortex as the tissues of acute inflammation would to free nerve endings in the periphery.

Everyone knows that stimulation of the sense organ gives rise to a central neural process, which in turn may be said to cause a conscious process. Our "mechanical neurophysiology" concludes that somatic neurons in the cerebral cortex have mechano-receptor specificity, and that physico-chemical changes at the synapse and other regions must be transformed into the form of mechanical stimulus energy if they are really and truely influencial in initial excitation. This is both a simple and a remarkable conclusion, and sounds strange to you unquestionably, but we may ask you to accept it or to find a positive fact about chemical transmission to the somatic neuron in natural environments. Electrical transmission to somatic neurons proved incorrect, and humoral transmission theory that exhibits the interrelation between some unknown chemical transmitter and some unknown chemical receptor is obviously a meaningless conception, because science is made up of confirmed relations among concrete events. The only remaining possibility is mechanical transmission, and mechano-receptor specificity of somatic neurons in natural environments, illustrated elsewhere in this paper, is firmly founded on facts and inexorable logic.

I have spent a great deal of time in searching for a lucid agent as the general stimulus for the initiation of depolarization of somatic neurons at the periphery as well as center, and found the mechanical energy as the best substitute for "mental power" in the customary sense. That the mental power is nothing but a mechanical power is the natural conclusion of mechanical neurophysiology. From this we have a new understanding of that science when well digested is nothing but good sense and reason.

VIII. Learning Mechanism

In learning, some change in the nervous system is necessary for new pattern of behavior to occur. This change has to appear and continue and disappear easily, and because of which previously unconnected parts of the brain must establish functional relations. It is very hard, or rather impossible, to adjust this sort of physiology to the speculation of a synaptic change (17) or of a new neural circuit.

Morphologic changes of the neuron do follow function, but they may have trouble explaining that learning which follows a single experience. In the nervous system, while the nerve cells show a series of degenerative change and many of them actually die and disappear, some neuroglial cells, particularly the perineuronal satellites, actually increase in number and appear to participate in the local processes.

The cells of a multicellular organism are conditioned mainly by adaptation to their specific function. Because of this functional specialization, all cells acquire specific characteristics. Irritability reaches its maximal development in animals. While special receptors adapted to receive the different types of stimuli are differentiated, the cells forming the somatic nervous system are differentiated to respond rapidly and specifically to mechanical stimuli originated in the outer and inner environments. On the other hand, oridinary non-neuronal tissues and the diffuse, non-specific nervous systems such as the sympathetic and the reticular activating system seem to be richly endowed as to receive stimuli of various sorts. The great ability of a human subject is, in a sense, due to the specific mechano-receptor property of the nerve cells forming the highly developed cerebral cortex. If the somatic neuron were to receive various kinds of stimuli in the body as is generally believed, everything should be thrown into terrible confusion. On the contrary, let it be that each somatic neuron has its own stimulus, then the existence of various kinds of receptors becomes meaningless. A final common stimulation of somatic neurons is therefore inevitable.

Morphologically and physiologically it is quite possible that a cortical neuron in the body is receiving ceaseless mechanical local stimulations from synaptic knobs and nonsynaptic structures. It goes then that synaptic mechanical transmission and nonsynaptic mechanical transmission are summative simply affecting the permeability of the membrane of the receiving neuron so as to make it easier for its axon to fire, and thus the real work of the cortex is going quietly behind the scenses by the pervaded and everchanging mechanical forces in the cortex.

The existence of mechanical transmission between neuron and neuroglial satellite cell has been detailed before. We do not feel the least hesitation in concluding that the augmentation of sites of the nonsynaptic mechanical transmission and strengthened adhesion of the glial satellite cell can be clearly identical as the repository of stored information.

Obviously learning must consist in the formation of an organized differentiated pattern of which selected response can be made. How do such organizations persist? To this question there is not even a wise speculative answer available at the present time. It now becomes easy to understand that the learned patterns persist in space not by new neural connection or lowered resistances of the synapse, but by new neuroglial satellite cells and strengthened adhesion of the neuroglial satellites.

In the living organism a higher degree of structure and function is maintained by a method of energy transformation based on continuous input and output of matter and energy. While recent years we have been spectators of the extraordinary development of molecular biology, it is again evident that these advances should be integrated within the framework of the cell as the true structual and functional organization of living matter.

Most of the capacity of the human brain is devoted to the unconscious autonomic regulation of the bodily processes without which life would fail. Our knowledge is still not enough to describe in detail how every cell is to be fabricated and connected with other cells of the body. In the normal waking state many of the cerebro-cortical neurons are in constant activity, whether signals are arriving or not. In fact, one may liken the conscious brain to a sheet of water constantly disturbed by the wind, with all sorts of ripples on its surface. What we can say now is that not all the cortical neurons are synaptically connected, but mechanical tension, pervaded in the brain, exerts excitatory influence upon them, so that unconnected parts of the brain can work separately or together according to the everchanging pattern of immediate mechanical stimuli in the cortex.

IX. Memory Mechanism

There is unmistakable evidence of the existence in the brain of specific memory mechanism, and one of the most important goals of present-day neurological research is the determination of the essential characteristics of the memory trace.

Most investigators feel that memory resides in the strengths of synaptic connection. However, microscopic observation of a synapse before and after neural activity to determine whether its physical dimensions have changed has not yet been found practical. Electro-chemical properties of the synapse before and after learning are even more difficult. Experimental work indicates that neural activity increases the amount of RNA in the nerve cells (18), but this kind of thinking about molecular changes of the memory trace is today highly speculative.

Although there is general agreement that the establishment of a memory trace involves physico-chemical changes in neuronal material, it is obvious that the first question of whether the neuron itself is the basic storage element is not answered. In humans, a multicellular organism, memory trace that poses one of the most severe problems faced by any theory of brain function seems to require a more potent factor to which storage capacity calculations are directly pertinent. It is by no means wise to identify human cortical neuron with a single protozoan cell or an autonomic ganglion cell in function.

Fortunately, the whole neurons are not the only possible candidate for designation as the basic storage element. There is another possibility. It is not necessarily true that the neurons and their interconnections are solely responsible for the unique properties of the brain. When viewed from the familiar natural immediate mechanical stimulus, it is probably our best assumption at present that the changes taking place in memory are predominantly the rearrangement of neuroglial satellites and new building of neuroglial satellites. We might say that maturation rigidly fixes the routes of neuronal circuits so that unlearned reflexes and responses can be altered little or not at all, and learning fixes the glia-neuronal routes flexibly so that learning and forgetting can readily be displayed.

Cerebro-cortical action is a thing apart from simple reflex activity. Sensory information is stored over long periods to appear in the cerebro-cortical output from time to time inextricably interwoven with more recent information. It is this property wihch underlies learning and memory. It is satisfying that we can explain this cerebro-cortical mechanism by a newly-organized pattern of familiar immediate mechanical stimulations of the neurons.

The sense of awareness is more real to the individual than anything else. The end product of the neuronal activity appears to be solely the stimulation of our sense of awareness. It is fairly clear to everyone that the sense of conscious recollection is automatically produced when specific groups of neurons in the brain are activated. The activation of a stored sensory patterns results in our conscious awareness of the contents of that pattern. Such activation will be our concern, but we shall not be concern with the means by which it produces our subjective sensations.

It may be that if a sufficient portion of the membrane of neurons for one of stored patterns is activated by synaptic or nonsynaptic immediate mechanical stimuli, the entire pattern fires. The point is the occurrence of immediate mechanical stimuli whether with or without synapses.

X. Image Producing Machanism in the Mind

Some author (19) states that the behavior is response to an image, and without the conception of an image the behavior cannot possibly be understood. The image acts as a field. He also says that the theory of the image is distinctly unfriendly to the position that facts and values are quite distinct, that facts are a proper subject for scientific study, whereas values are not, that facts are objective and values are subjective. In the theory of image, images of fact and images of value are alike present in the image. Other says that introspection is a method of the observation of certain events in the brain (20). We can supplement one thing to such semantics that field is the field of some physical energy, and in the cerebral cortex fact and value have some specific pattern of mechanical stimuli in common.

The information concept as we have it in neurophysiology is confined to an extremely limited level of abstraction. It is still quite incapable of dealing with semantic content, but, on the contrary, any abstraction becomes a scientific event when considered from the standpoint of the pattern of adequate mechanical stimuli produced in the cortex after the image of the contents of that abstraction. The field of an image is thus embodied by the field of mechanical energy. As is proved by the experiment with isolated single nerve fiber and hydrostatic pressure, mechanical energy is effective only when it is localized on the neuronal membrane, and this is actually fulfilled by the intercellular attachment devices.

We must frankly cofess that the data available for the physiology of higher functions are still scattered, fragmentary and incomplete. Aristotle, 2,000 years ago, was asking how is the mental power attached to the body. We are asking that question still. We know that loss of the brain produces loss of mind. We now see that cerebro-cortical neurons do not work without immediate mechanical stimuli occurring in the cerebral cortex in a similar way at the periphery.

The purpose of this paper was to propose "mechanical physiology" of the somatic nervous system which is unquestionably tenable. It now seems that the time has come to lessen the sad gaps which hitherto seemed impassable in the region lying between psychology and neurophysiology. Knowledge was never more useful than it is today and peoples all over the world have at last awakened to the fact that unless they absorb science they are doomed. It is perfectly obvious that the best way is to abandon conventional notions that cause hindrance, and to accept new scientific ideas that produce progress in order to get out from the present difficult situation that most neurophysiological problems of vital importance, such as mechanisms of pain, learning, and memory, remain unsolved in spite of the tremendous amount of careful, painstaking research.

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