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A New Hypothesis for Electrical Transmission in the Mammalian Central Nervous System

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Abstract — It has been previously shown that the anatomical synapse does not exist in the living central nervous system, and that receptors are unlikely to be unique molecules sited on particular locations in or on the cell membrane. These conclusions and the rapidity of action of intravenously administered substances necessitated the adumbration of a new electrical hypothesis for the mechanism whereby signals pass from one part of the brain and spinal cord to another. The hypothesis proposed implies some testable predictions.

Brief historical summary on transmission

In 1897, Sherrington proposed the physiological concept of the synapse (1, 2, 3), and soon afterwards Held saw 'end-fusse' on neurons in the trapezoid nucleus of cat, dog and rabbit. 'I shall designate (them) physiologically simply as zones for the transmission of stimuli' (4). Bernard demonstrated the dissociation of nerve and muscle activity by curarising frogs (5), and this is regarded as one of the key experiments in the development of the concept of chemical transmission. The observations that the actions of adrenalin and sympathetic stimulation were similar (6), as were acetylcholine and parasympathetic stimulation (7, 8) further supported this idea.

During the first half of the 20th Century, the alternative view, that transmission was electrical, enjoyed wide support, mainly because the electrical properties of what are now called conduction and transmission were seen to be similar (9, 10, 11). At about the same time, the belief gradually gained currency that findings from the neuromuscular function were relevant not only to autonomic, but also to central synaptic, transmission. 'The original hypothesis was made as general as possible by applying it to the neuromuscular functions of skeletal muscle, and to the synapses of the sympathetic ganglia as well as of the central nervous system', wrote Eccles (11). This assumption has been almost universally accepted.

Katz and his collaborators studied the frog neuromuscular function by intracellular recording and electron microscopy. They concluded that transmission across it was chemical (12), except for some invertebrate synapses (13, 14). Both the current chemical hypothesis and the previous electrical hypothesis (11, 15) start off with the belief in the existence of the anatomical synapse in the living mammalian central nervous system. It should

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be stressed that the hypothesis to be presented addresses the question of transmission in the central nervous system only, and does not share the assumption that its properties are the same as in other junctional tissues.

Introduction to new hypothesis

Detailed evidence has been published that: (a) the central anatomical synapse probably does not exist in life (16), although there is no reasonable doubt about the physiological properties attributed to synapses; (b) receptors are probably not unique molecules located at discrete regions of the neural, synaptic or target cell membranes (17); (c) the central nervous system is largely composed of neuroglia, or 'nerve-glue' in the original sense of Virchow (18), that is, it is a syncytium composed of a ground substance enclosing relatively few neurons (19, 20, 21); and (d) many of the experiments designed to localise receptors by histochemical, electron microscopical, immunocytochemical and subcellular fractionation techniques, have never been controlled in respect of the possible effects of the procedures on the properties of the organelles being studied. Therefore, such experiments are incomplete, and it would be premature to draw conclusions from them (22, 23, 24).

Nevertheless, there is overwhelming evidence that signals do pass from one part of the central nervous system to another in the living animal. Therefore, serious reservations about important elements of current views induce an obligation to formulate alternative, testable hypotheses.

Previous evidence

The following additional findings have also been used as the bases for the new hypotheses: (e) the concept of the blood brain barrier arose from the delay in arrival of dyes, ions, sugars and aminoacids in the brain (25 – 30); (f) anaesthetics, analgesics, analeptics, tranquillisers and other neuroactive substances, when injected intravenously, spread through the circulation in 0 – 12 s, and act on the central nervous system within seconds to minutes later (31 – 35); (g) cerebral and spinal capillaries are spaced 60 μm or more apart in adults, as measured in stained tissues, which are shrunk (36, 37), so that the real intercapillary distance may be much higher. Thus substances entering the brain from the blood would have to pass through the cerebral or spinal capillary membranes, and then the choroid plexus or the full length of the neuroglial cells before reaching the excitable cells (38 – 41); (h) cells presumed to be neurons are excited or inhibited by the extracellular application of transmitters and aminoacids (42 – 45); (i) lack of oxygen or substrate depolarises cells (46 – 50); (j) changes in the direct current potential differences across parts of the nervous system or individual cell membranes affect their excitability (51, 52, 53); (k) there is a potential difference between the cerebral blood vessels and the brain substance (54 – 58); (l) the conductance of the intact brain is greater than that of the membranes of the cells within it (59, 60, 61); (m) the concentrations of ions in the interstitial fluid of the brain are remarkably constant (62, 63); (n) non-synaptic transmission has been reported in a wide variety of mainly invertebrate tissues (13, 14). This has usually been assumed to occur at 'tight' junctions (64, 65), but this localisation cannot be proved directly; (o) electrical signals can be conducted through biological tissues without crossing synapses, for example, when an electrocorticograph or an electroencephalograph is recorded, or when extracellular stimulation or recording is made in relation to a neuron or a peripheral nerve; and (p) many drugs in clinical concentrations have high affinities for plasma proteins (66).

Assumptions of the proposed hypothesis

1. Electrical signals can be conducted more rapidly through tissues than molecules can move by diffusion, passage across membranes, or as a consequence of enzyme reactions.
2. The capillaries penetrating throughout the central nervous system are the sites at which all rapidly acting substances have their effects.
3. There are no membranes between the capillaries and the neuroglia, or 'interstitial' compartment.
4. Rapidly acting neuroactive substances affect the electrical properties of the capillary membrane, and thus initiate an electrical impulse, which 'broadcasts' rapidly in all directions across the neuroglia to the nearest dendrites and somas, acting as aerials (Fig. 1).
5. The electrical impulse gradually dissipates in

the conductive neuroglia, with a speed and to an extent depending upon its chemical composition at that particular moment. The response of excitable cells to a stimulus depends upon the sensitivity of their membranes at that particular moment.

6. The particular routes of physiological signals between neurons is a consequence of their anatomical relationship to each other in a topographical sense, similar to the localisation of the sensory and motor cortices in the tracts and brain.

Train of events following intravenous injection of a rapidly acting neuroactive substance, T

T circulates within 9 – 12 s. Meanwhile, it partitions between the plasma, the blood cells and the endothelia of the blood vessels on the way, generally in favour of the plasma (Fig. 1).

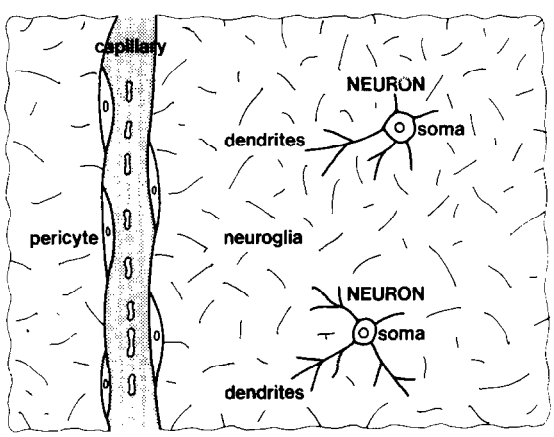

Fig. 1 Diagram showing the route of passage of the electrical excitability caused by the neuroactive substance acting on the membrane of the cerebral or spinal capillary, on the left. The electrical signal passes across the neuroglia to the dendrites or somas of the nearest neurons, on the right. For a description, please see the text.

T spreads rapidly through the total network of capillary membranes of the central nervous system. The network possesses a considerable resistance, impedance and capacitance. The capillary membranes are extremely thin in life, even when pericyte nuclei adhere to them, so that it is likely that the potential difference of the blood-brain barrier is across the total capillary wall thickness, rather than between the blood and outer capillary membrane into the capillary cytoplasm, with a further potential difference between the cytoplasm across the inner capillary membrane into the neuroglia.

If T is of the right chemical configuration, it affects the resistance, impedance or capacitance of the capillary membrane. A transient electrical signal is induced at the capillary membrane-neuroglial interface (Fig. 2). The electrical signal is conducted in every direction through the low resistance neuroglia. The transient is not self-regenerative, and so it decrements within the volume of the neuroglia.

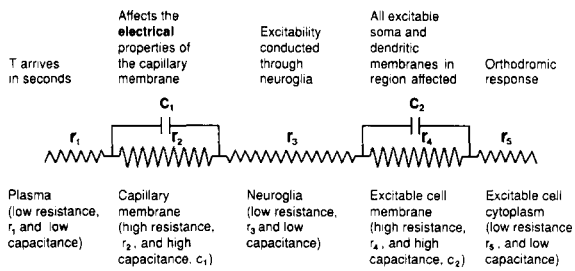

Fig. 2 The equivalent circuit showing the passage of the electrical excitability from the capillary, on the left, across the capillary membrane and the neuroglia to the excitable cell membrane, on the right. The capacitances of the plasma, the neuroglia and the cytoplasm are assumed to be small, and are not shown.

The direct current potential difference across the tissue determines the excitability of the particular region of the brain or spinal cord. It could be the cause of the 'central excitatory' and 'central inhibitory' state of Sherrington (67, 68).

The 'broadcast' impulse is picked up by all the dendrites and somas in the region and decrements in the low resistance neuroglia (Fig. 1). Large enough, or several, impulses excite the dendrites or cell bodies in the region, and an orthodromic stimulus is initiated down the axon. Preformed discrete receptors do not exist on the soma or dendrites, but the whole, presumably soma-dendritic, membrane, is sensitive to electrical activity and substances which act rapidly on the central nervous system. According to a hypothesis previously proposed (17), the inherent characteristic of the excitable membrane is the range of substances to which it reacts by altering physico-chemical properties.

Predictions of the proposed hypothesis

1. T is found in relatively high concentration in the capillaries, but in extremely low or undetectable concentration adjacent to cells — upon which it acts if added iontophoretically, — as soon as it produces an effect.
2. The cerebral and spinal capillaries have a high affinity for T.
3. T affects the electrical, but not the chemical properties of the capillary membranes, before it can have any effect on excitable cells in the brain or spinal cord. Therefore, an electrical signal should be detected between the capillary and the excitable cell, before that cell fires.
4. Brief periods of natural physiological stimulation in vivo do not produce detectable biochemical effects.
5. Substances acting within a few seconds of administration cause their effects by reacting within the capillary membrane. Substances taking longer could affect the chemical or electrical properties of the neuroglia.
6. The properties of the blood brain barrier are relevant to slower events in the central nervous system, such as partitioning of T within the different compartments, affinity for the chemical constituents of the latter, the reaction of T with the latter (including its metabolism), and excretion of T and its metabolic products.

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