PONTIFICIA ACADEMIA SCIENTIARVM

COMMENTARII

VOL. I N. 18

J. C. ECCLES

RESEARCHES ON THE CENTRAL NERVOUS SYSTEM

EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

PONTIFICIA
ACADEMIA
SCIENTIARVM

COMMENTARII
Vol. I - N. 18
pag. 1-16

RESEARCHES ON THE CENTRAL NERVOUS SYSTEM

J.C. ECCLES
Pontifical Academician

SVMMARIVM — Auctor, postquam nervearum cellularum structuram examinavit earumque electrica potentialia diversis experimentis perpendit, exponit quid concludi possit ex investigationibus, quas per hos duos annos fecit ad determinandas functiones et diversas praesynaptici et postsynaptici mechanismi species.

The human brain is the most complex organization of matter in existence, though of course the brains of higher animals are not greatly inferior. It is expedient for certain purposes to consider it as analogous to a machine; but it is of different order from any machine designed and made by man. Furthermore nothing is given, there are no diagrams of operation, no maker's instructions! In our task of trying to understand it, we firstly can examine its structure and then attempt to discover the mode of operation of the simplest components. Each of these two modes of investigation, morphological and physiological is complementary to the other.

This highly magnified section of the cerebral cortex (Fig. 1) shows many nerve cells, which are the morphological and physiological units that make up the nervous system. Each nerve

Communication presented on October 4, 1962, during the Plenary Session of the Pontifical Academy of Sciences.

cell is a complex structure with many branches, called dendrites, that receive information from other nerve cells and one other fine branch, the axon, that transmits messages or impulses to other nerve cells. This section gives some idea of the complexity of association of nerve cells with nerve cells, but even this picture is greatly simplified from reality, because by a special procedure less than 2% of the cells were stained. It has been estimated that there are about 10^{10} nerve cells in the humain brain, and each nerve cell would directly receive information from many nerve cells, and in turn transmits information to a like number, often to hundreds.

In this reconstructed model of a nerve cell with its dendrites and axon represented merely by stumps (Fig. 2), it is seen that there are numerous small knob-like endings on its surface. These are, in fact, the endings of axons of other nerve cells, which in this way hand on information to this nerve cell. Each nerve cell is an independent unit completely enclosed by a surface membrane 50 to 100Å thick; and communication between nerve cells occurs at these numerous areas of close contact or synapses as they were first designated by SHERRINGTON. As we shall see later, there are special processes of interaction between the localized reactions produced on nerve cell by these synapses. In contrast the transfer of information from the nerve cell along its axon is conveyed as brief electrical messages or impulses that travel from the cells down all the numerous branches of the axons, so reaching finally the synaptic contacts with other nerve cells. Transmission across synapses is effected by the secretion of minute amounts of specific chemical substances. During normal activity any one nerve cell is continuously bombarded by impulses impinging on its synapses. Under certain circumstances which we will now proceed to consider, this integrated synaptic bombardment on a nerve cell will cause it in turn to fire impulses down its axon and so transmit information to other nerve cells. When not discharging impulses, a nerve cell is of course transmitting no information.

Evidently it is of great interest to study the manner in which synaptic bombardment on a nerve cell causes it to discharge impulses down its axon. Since we first developed the technique of recording electrically from the interior of nerve cells in 1951, there have been systematic investigations on many varieties of nerve cells using this technique of intracellular recording by fine glass micro-electrodes. There has been ample confirmation of the original discovery that there are just two kinds of synaptic action on a nerve cell. Normally the inside of a nerve cell is about 70 mV negative to the outside, this being the electrical potential across its enclosing membrane. When one type of synapse is activated, it reduces this resting polarization of the membrane (Fig. 3). If this depolarization is as large as 10 mV, the membrane potential being reduced to - 60 mV, the nerve cell is caused to generate an impulse which is discharged down its axon; so eventually there is activation of the synapses that it makes on other nerve cells. Activation of the other type of synapse has an opposed action, increasing the polarization of the membrane (Fig. 3). It very effectively counteracts the depolarizing synapses and so inhibits them from generating the discharge of impulses. The actions of these two types of synapse, respectively the excitatory and inhibitory, have been investigated in great detail in order to discover their modes of action. Some of the simpler investigations are illustrated in the diagrammatic neurone of Fig. 4. The most important finding is that both excitatory and inhibitory synapses act by causing a momentary large increase in the membrane permeability to certain ions: potassium and sodium for excitatory synapses; chloride and potassium for inhibitory synapses.

The interaction of the potential changes produced by excitatory and inhibitory synapses is shown as recorded by the microelectrode to the right of Fig. 4. The upper row of records illustrates the interaction of the excitatory and inhibitory potentials, while in the lower row it can be seen that the inhibitory synaptic action prevents the generation of impulses by the

excitatory synapses. So far as the nerve cell itself is concerned there is general agreement that these two basic modes of synaptic action govern the generation of impulses by the cell. The actual behaviour of a cell from instant to instant results from the integration of these two opposing actions, an excess of depolarization causing a discharge whenever it occurs. Only under such circumstances is the cell acting as a channel of communication; otherwise it is silent with zero function.

Fig. 4 illustrates also a third mode of synaptic action in the central nervous system which we have been studying during the last three years. Our physiological experiments led us to postulate that there are synaptic endings on excitatory synaptic knobs os shown in the upper part of Fig. 4, and now several electron-microscopists have discovered these structures exactly as predicted. These chemically transmitting synapses act by depolarizing the excitatory synaptic knobs, so diminishing the sizes of impulses in these knobs and their release of excitatory transmitter substance. As a consequence there is depression of the depolarizing action of the excitatory synapses and this may prevent or delay the generation of impulse discharge as shown by the upper series to the left, this synaptic mechanism thus having an inhibitory action. Since this inhibitory action is exerted on the excitatory *presynaptic* terminals, it is called *presynaptic inhibition*; in contrast, the inhibitory action diagrammed in Fig. 3 and to the right of Fig. 4 is exerted on the postsynaptic membrane and so is called postsynaptic inhibition.

One of the tasks we have been engaged on in the last two years has been to identify the inhibitory actions at various places in the central nervous system as being of the presynaptic or postsynaptic types.

In investigations on the mode of operation of the simplest pathways in the central nervous system, one very important principle is being discovered at every level, the principle of negative feedback. Fig. 5 demonstrates the simplest example. The axons of the nerve cells that innervate muscle fibres give

off one or more branches before they leave the central nervous system. Impulses discharged to the muscle also travel back along such axon-collaterals and excite special inhibitory cells, Renshaw cells, to discharge impulses that in turn have a widely distributed inhibitory action on nerve cells that innervate the muscles of that limb. Evidently the discharge of impulses to muscles also activates the inhibitory pathway through Renshaw cells that tends to depress this discharge, so exercising a simple negative feed-back control on the discharge.

Fig. 6 gives an example of how presynaptic inhibition produces a very effective negative feed-back on all flow of information from cutaneous receptors into the central nervous system. The impulses coming into the spinal cord along the nerve fibres labelled C cause the C nerve cells to discharge impulses which in turn travel along axon collaterals to the D cells that have presynaptic inhibitory endings on the synaptic terminals of the C fibres. This presynaptic inhibitory action is very widely distributed, so that impulses coming from the cutaneous receptors on any part of a limb turn down the excitatory action not only of themselves, but also of impulses from all parts of the skin of that limb and even of the contralateral limb. Fig. 6 shows that many types of receptors from muscle also contribute to the presynaptic inhibition of cutaneous afferent fibres.

Finally Fig. 7 illustrates diagrammatically the manner in which negative feed-back operates on the pathways of such cutaneous sensations as touch and pressure. There are just two synaptic relays on the main pathway, one in the dorsal column nuclei and the other in the thalamus. We have been studying the inhibitory controls exerted at these two synaptic relays. In both cases the inhibition has the widespread diffuse action that is appropriate for negative feedback. In the dorsal column nuclei it is mostly of the presynaptic types, whereas in the thalamus it is mostly postsynaptic.

I will conclude with an attempt to give a general under-

standing of the significance of negative feed-back on sensory pathways up to the brain. It is important to realize that there is an enormous amount of background discharge from receptor organs and also that the information from any one focus is conveyed very diffusely with wide overlap. Yet somehov we perceive clear and sharp sensations despite all these imperfections in the pathways of communication.

At each of the synaptic relays on the pathway, the negative feed-back produced by any strong input depresses not only that input, but all the diffuse background of what we may call sensory noise. The result is an increase in the signal to noise ratio and a sharpening of the signal that is transmitted on to the next relay, where there is a similar processing of the signal and so on. In this way the brain is safeguarded from the confusion of trivial information that flows into the central nervous system from the multitude of receptor organs. Furthermore, sufficiently discriminative examination discloses many aberrant nerve connections, which would, of course, be expected to arise during the process of growth and development. The disorders of transmission that could arise in this way are also eliminated by negative feed-back.

These few over-simplified ideas on the working of the nervous system at least will serve to show that there have been some significant advances in our efforts to understand this most complicated structure. Fortunately there are these few encouraging facets, but the immensity of the task is beyond all imagination.

FIG. 1 — Section of the cerebral cortex in which about 1.5% of the cells were stained by the Golgi-Cox method. Note the many large pyramidal cells with their branching dendrites. (Personal communication by D.A. SHOLL).

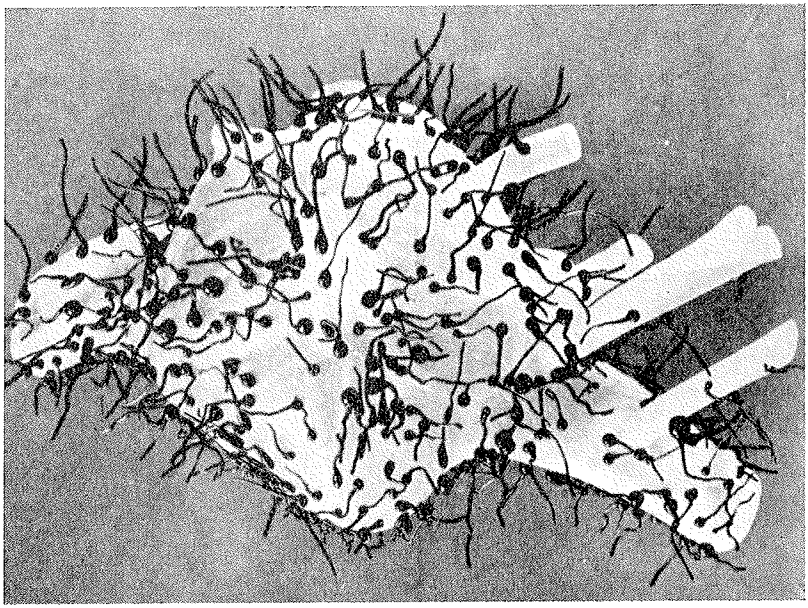

FIG. 2 — Model of body and large dentritic stumps of a mammalian neurone reconstructed from serial sections by R.A. HAGGAR and M.L. BARR.

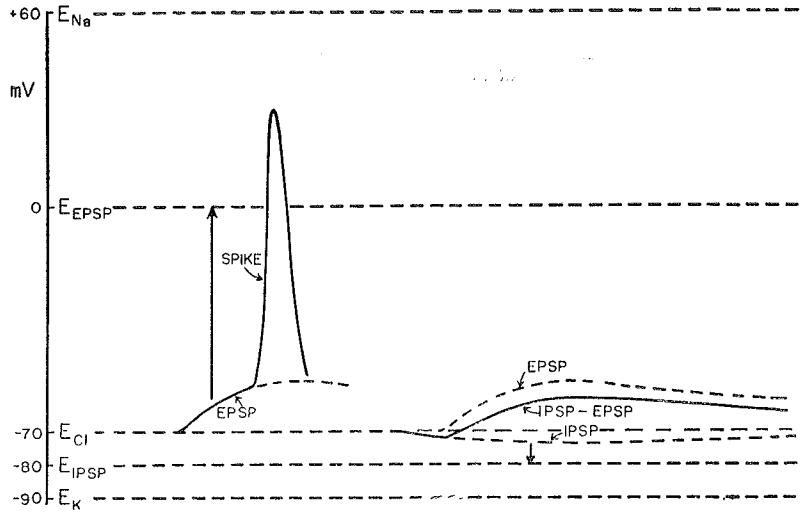

FIG. 3 — Potentials recorded inside a nerve cell, there being a resting interval potential of −70 mV. Initial upward deflection is due to excitatory synaptic action (EPSP) which generates the large spikelike potential or impulse when it exceeds about 10 mV, *i.e.* when the internal potential is reduced to −60 mV, the broken line showing the true course of the potential if it fails to generate a spike. In the right hand part of the diagram inhibitory synaptic action (IPSP) is seen to increase the polarization of the membrane and in this way it diminishes the size of a superimposed excitatory action (broken line) and so prevents it from generating an impulse.

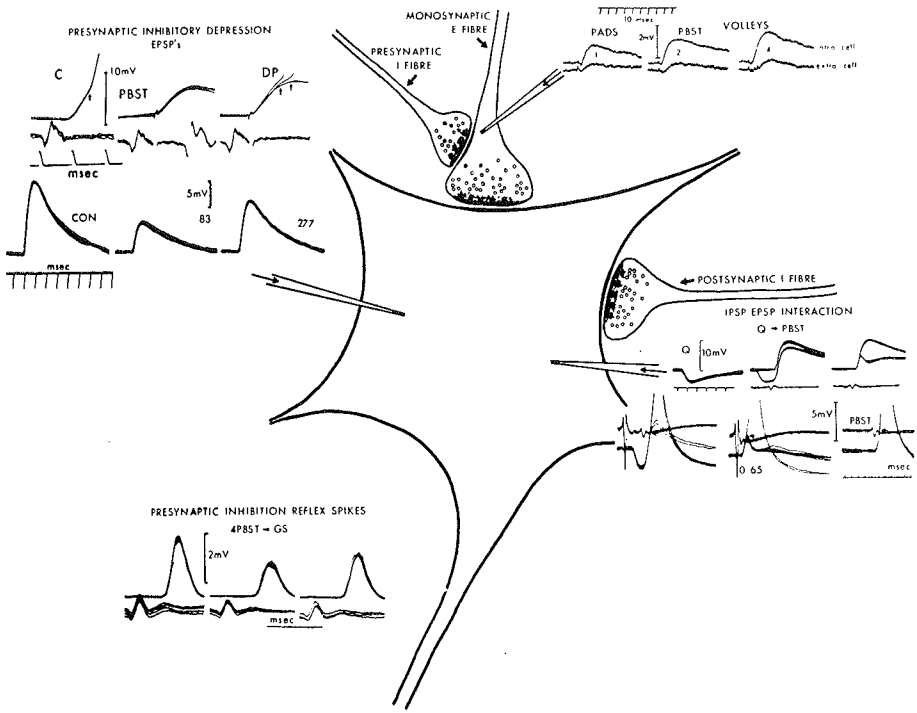

FIG. 4 — Composite diagram showing specimen records of the various types of responses associated with synaptic action. On the right side is an intracellular electrode with specimen records of IPSP's (downward deflections) and EPSP's (upward deflections) and their interactions, there being two examples of spike inhibition in the lower row. Exitatory and inhibitory synapses are shown on the neurone and also a presynaptic inhibitory ending on the excitatory fibre, which by intracellular recording (note electrode) is seen to be depolarized, as shown by the difference in the intracellular and extracellular records in the upper right traces for 1, 2 and 4 volleys. In the upper left quadrant are the effects of this presynaptic depolarization on its excitatory synaptic action (EPSP) as recorded intracellularly. Note the large diminution of the excitatory potentials in the lower row. In the upper row the presynaptic inhibition depresses the excitatory potential so that it often fails to generate a spike, as it regularly does in the control (C record) at the arrow. In the lower left quadrant is seen the resultant diminution of the reflex spilke discharge recorded in the ventral roots, the first being the control response.

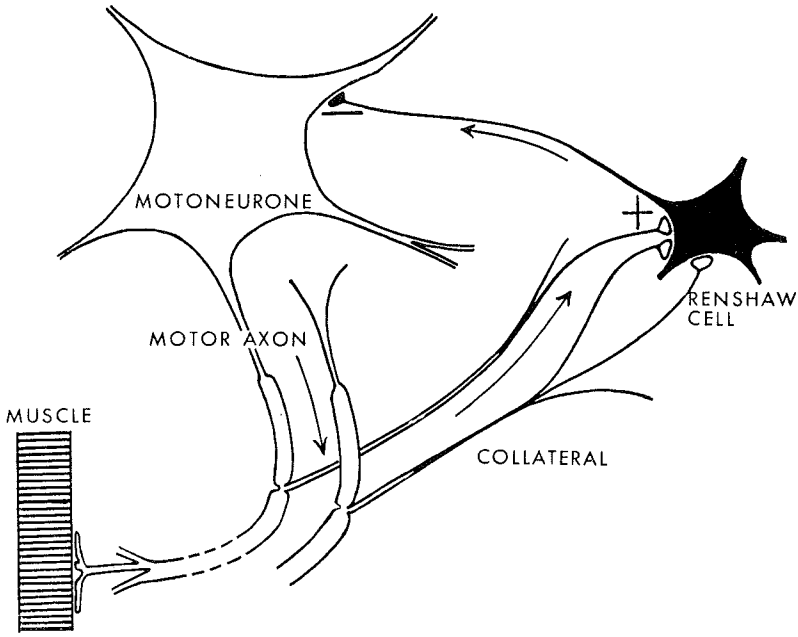

FIG. 5 — Schematic drawing of a nerve cell whose axon (motor axon) passes out to the peripheral to innervate muscle fibres. The axon also gives off a collateral branch that forms excitatory endings on a special type of inhibitory cell, called Renshaw cells, and there in turn send their axons to form inhibitory synapses on motor nerve cells.

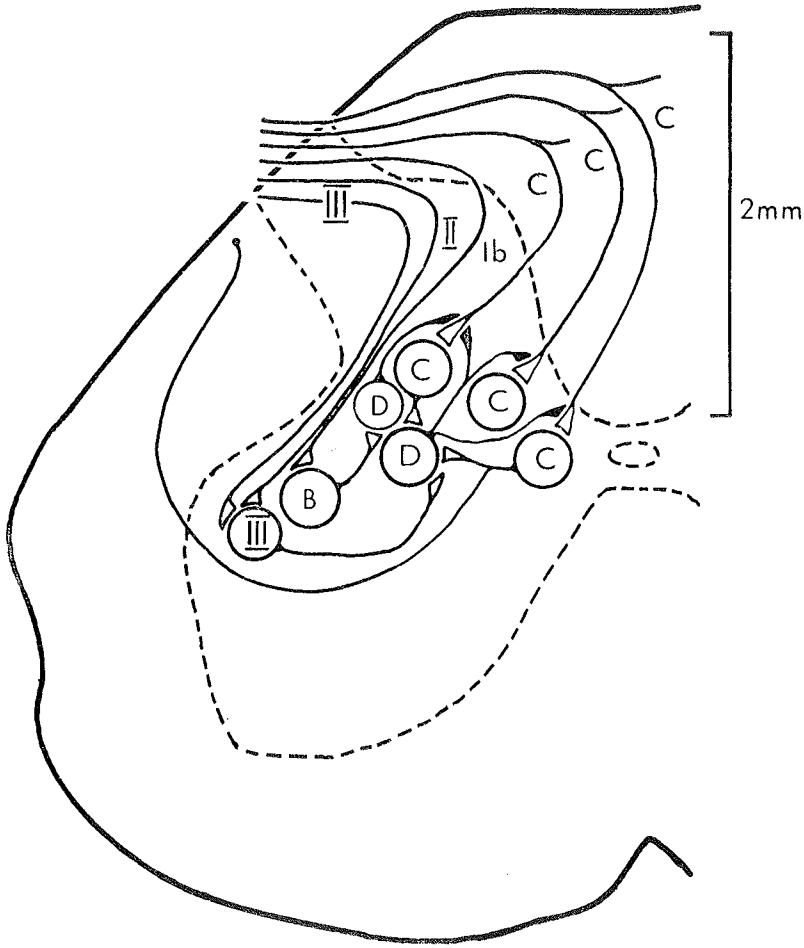

FIG. 6 — Diagram of transverse section of spinal cord showing the postulated central connections on cutaneous afferent fibres (C) and the recurrent inhibitory pathway through special interneurones (D) back to give presynaptic inhibition on the synapses of these C fibres. Some types of afferent fibres from muscle (Ib, II and III) are also shown contributing to the presynaptic inhibition.

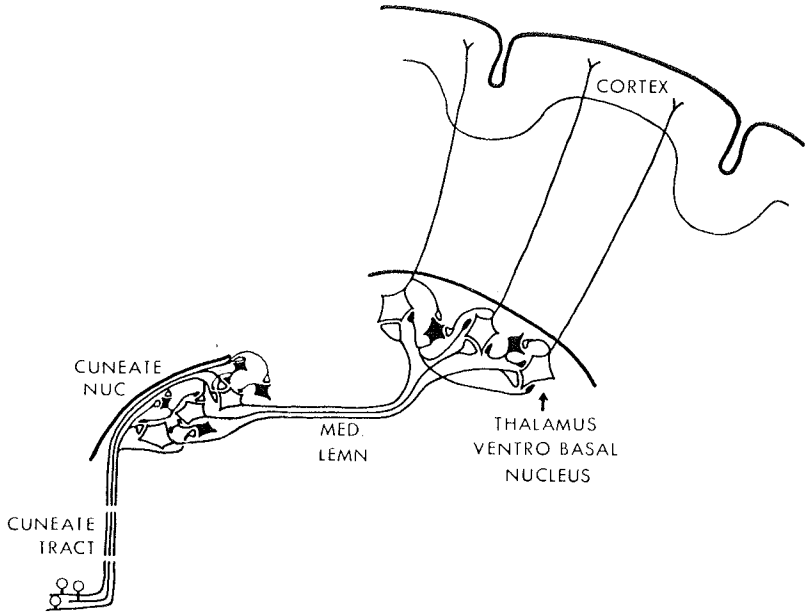

FIG. 7 — Diagrammatic representation of pathway from cutaneous fibres to the fore-limb up to the cerebral cortex. The first synaptic relay in the cuneate nucleus is seen to be subjected both to presynaptic and postsynaptic inhibition, whereas the second synaptic relay in the thalamus is subjected to a very powerful postsynaptic inhibition that operates via axon collaterals such as in Fig. 5.