SIGNIFICANCE OF THE INHIBITORY SYNAPSES IN THE MECHANISM OF COMPENSATION FOR IMPAIRED FUNCTION

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Eccles et al., [5, 6, 8, 9, 10] have shown that strychnine and tetanus toxin block inhibitory synapses and eliminate all kinds of postsynaptic inhibition in motor neurones of the spinal cord. This discovery enables strychnine and tetanus toxin to be used extensively to reveal the role of inhibitory synapses in normal and pathological reflexes.

The experiments described below show the part played by inhibitory synapses in reactions caused by the very widespread pathological process - inflammation.

EXPERIMENTAL METHOD

A subcutaneous injection of 0.2 - 0.5 ml of turpentine into one of the hind feet of an animal was given in order to produce an inflamed area. We studied the changes in the nervous system which developed along the nervous pathway of the impulses from the inflamed area, and for this purpose we investigated spinal mono- and polysynaptic reflexes, the primary responses in the specific thalamic nucleus (VPL), the primary responses in the cortical representation in the inflamed organ - in sensory areas I and II [1, 2].

To suppress the activity of the inhibitory synapses strychnine was injected intravenously as follows: to study mono- and polysynaptic reflexes the dose was 0.05 mg/kg, and for investigation of the primary thalamic and cortical responses it was 0.5 mg/kg.

EXPERIMENTAL RESULTS

As we have shown previously [1] and as the present experiments have confirmed, impulses from the inflamed area cause an increase in the amplitude of the spinal mono- and polysynaptic flexor reflexes. Impulses from the inflamed area cause similar changes in the central nervous system at higher levels [2]. The primary responses in the specific thalamic nucleus (VPL) are enhanced as are also the primary responses in the cortical responses in the cortical representation of the inflamed area - in sensory areas I and II.

The occurrence of a discharge in a nerve cell depends upon the magnitude of the membrane potential. Increase in the amplitude of the spinal, thalamic, and cortical responses under the influence of impulses from the inflamed area is evidently the result of the involvement of a large number of neurones in the reflex reaction. We may therefore, suppose that the essential feature of the changes evoked by impulses from the inflamed area is that it brings about a depolarization of neurones with the result that they are more readily discharged, and a greater number of them are involved in the response to the test stimulus.

These results throw new light on one of the most characteristic features of pathologically altered organs - their increased sensitivity to ordinary stimuli. It is known that during inflammation a limb will be sharply withdrawn in response to a lighter touch than is normally required. In inflammatory processes in the lungs or heart a moderate degree of physical exercise will cause considerable dyspnea and tachycardia. In gastric ulcer there is an abnormal increase in secretion in response to an adequate food stimulus, etc. Evidently, in these cases impulses originating in pathologically altered tissues bring about a reduction in the membrane potential of neurones which regulate the

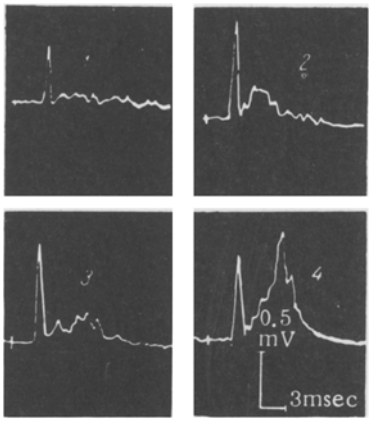

Fig. 1. Mono- and polysynaptic reflexes from a damaged foot (3) are more marked than the mono- and polysynaptic reflexes from the undamaged foot (1). Injection of strychnine causes a greater increase in the polysynaptic reflexes from the damaged limb (4) than from the healthy limb (2). Stimulation applied to the common peroneal nerve; stimulus supramaximal for the I group of fibers.

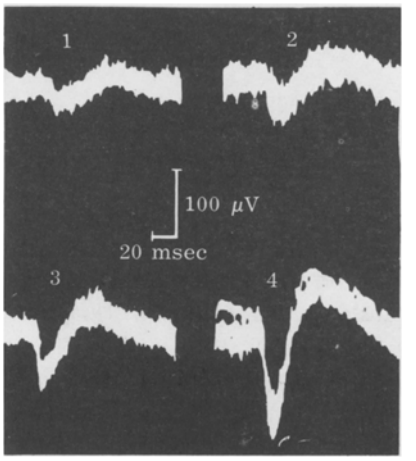

Fig. 2. Primary responses of the specific thalamic nucleus (VPL) from the damaged limb (2) are more marked than from the undamaged limb (1). Injection of strychnine causes a greater increase in the primary responses from the damaged limb (4) than from the undamaged limb (3). Each record represents the supraimposition of 5 traces. Stimulation applied to the superficial peroneal nerve.

activity of the organs concerned. As a result these neurones are more readily discharged when an adequate stimulus is presented, so that their reaction is enhanced, just as we have found it to be in our experiments.

The injection of strychnine into animals having an inflamed area in one of the hindlimbs caused a marked increase in polysynaptic reflexes (most marked in the flexor reflexes both on the healthy and on the damaged side. However, in 14 out of 15 experiments the increase in the polysynaptic reflexes on the damaged side was 100-200% greater than in the healthy limb (Fig. 1). The selective increase in the polysynaptic reflexes leads us to suppose that strychnine blocks chiefly the inhibitory synapses of the interneurones.

We have already mentioned that impulses from the inflamed area by themselves (before the injection of strychnine) bring about an increase in the mono- and polysynaptic flexor reflexes. However these changes are not apparent until the 3rd-4th day after damage to the limb. In the first few hours or even days after damage to the foot the changes in the mono- and polysynaptic reflexes were varied in nature [1]. Here it is particularly interesting that the effect of the action of strychnine, even in the first few hours after damage to a limb, was entirely consistent: the polysynaptic reflexes from the damaged limb were always considerably more enhanced than they were from the healthy limb. In the period immediately following the damage the individual variations of the mono- and polysynaptic reflexes may have been related to the degree of activity of the inhibition synapses in the particular animal.

The primary responses in the VPL and in the somato-sensory cortical areas evoked by stimulation of the superficial peroneal nerve were also increased by the injection of strychnine. Here the effect was much better shown when the nerve on the damaged side was stimulated; in the contralateral hemisphere the responses were increased by twice as much as in the ipsilateral hemisphere Figs. 2 and 3). In many of the experiments secondary responses which had not been seen previously occurred in the contralateral hemisphere (see Fig. 3).

It is important to note that no facilitatory influence of strychnine of the primary cortical responses following stimulation of the VPL could be found. This result is in line with the most recent investigations of Eccles et al. [4, 7], who found that not all inhibitory cortical synapses are blocked by strychnine. Apparently, the facilitatory influence of strychnine on the thalamic and cortical responses (which are best shown in the contralateral hemisphere) are caused by a corresponding facilitation evoked by strychnine at a subthalamic level.

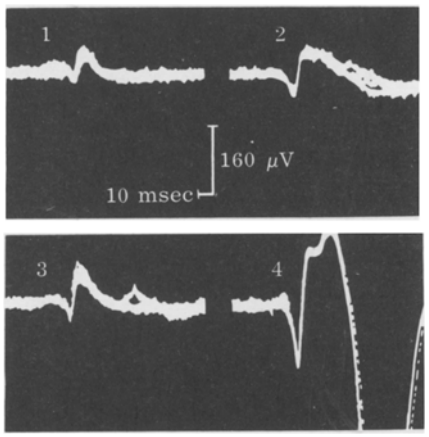

Fig. 3. Primary responses in area I of the sensory cortex originating in the damaged limb (2) is more marked than when the origin is in the undamaged limb (1). Injection with strychnine causes a greater increase in the primary responses from the damaged (4) than from the undamaged limb (3). In addition to the primary response from the damaged limb there is a secondary response. Each record represents the superimposition of 5 traces. White dots indicate moment of stimulation. Stimulation applied to the superficial peroneal nerve.

Therefore, strychnine causes a marked increase in the spinal, thalamic, and cortical responses along pathways followed by impulses from the inflamed area. We may, therefore, draw the following conclusion which is important for an analysis of pathological reaction.

The degree of involvement of neurones of the spinal cord, of the cortex and of the subcortical nuclei in reactions evoked by an inflammatory process is determined by the activity of the inhibitory synapses. When these synapses are blocked by strychnine a far greater number of neurones may be involved in the pathological reaction. Evidently the greater the flow of impulses into the central nervous system from the inflamed area the more these impulses will be inhibited. Elimination of the activity of the inhibitory synapses is all that is needed to reveal an abnormally large pathological reaction.

An additional cause of the same effect is that under the influence of impulses from the inflamed area the neurons may come to be in a condition of subthreshold depolarization with the result that blockade of the inhibitory synapses facilitates their discharge.

When the increase is very great the reactions to stimulation from the inflamed area may cease to exert their adaptive biological function, and become harmful. This conclusion is completely in line with the observations set forth below.

Even at the end of the last century Sherrington had shown that the brain stem between the anterior and posterior colliculi induces a marked increase in the response to proprioceptive impulses, with the result that the tone of the skeletal muscles was enhanced (the extensors were chiefly affected), and decerebrate rigidity develops. As our previous experiments have shown [3] the response to impulses from tissues altered by inflammation is superimposed upon this condition. In decerebrate rigidity the flexor reflex from the damaged limb may not only be enhanced (development of a flexor instead of an extensor rigidity), but, what is more interesting, in many experiments relaxation of the rigidity occurs in the healthy limb opposite the damaged limb. Normally this additional feature of the reaction remains hidden and compensated. Were this not the case, in man any abscess on the hand might result in disablement. Even more interesting was the result in many experiments in which the inflammation on the foot had already ceased, so that the animal walked normally; here, decerebration induced in the damaged limb not an extensor but a flexor rigidity. Hence, it follows that recovery was brought about not only by cessation of the peripheral inflammation but also by suppression of the residual effect in the central nervous system.

The fact that these observations could be made in the presence of decerebrate rigidity now acquires considerable significance. Sherrington compared decerebration with the action of strychnine on the nervous system, which is now known to depend upon blockage of inhibitory synapses. Thus, as these experiments have shown, elimination of the activity of inhibitory synapses may indeed lead to enhancement of the pathological reaction, and to the involvement of undamaged organs; finally there may be recurrence of the impairment of function when inflammation in the periphery has already subsided.

As a whole the results reported indicate that the activity of the inhibitory synapses is one of the most important compensatory mechanisms, or as I. P. Pavlov liked to describe it graphically, it is " a physiological defense mechanism." The establishment of this compensatory mechanism in reactions evoked by a most widespread pathological process - inflammation, whose significance had not even been suspected until recently, will be likely to be reflected in therapeutic measures.

SUMMARY

Strychnine blocks inhibitory synapses and enhances spinal polysnyaptic reflexes [5, 6, 8, 9, 10]. An identical effect was produced in an animal with an inflamed area in one hindleg by intravenous strychnine; there was, however, the important difference that on the affected side the amplitude of the polysynaptic reflexes was 100-200% greater than on the other.

Also, there was a more pronounced facilitation in primary responses in the VPL of the thalamus and in the somato-sensory cortical area on the side opposite to the damaged limb (Figs. 2, 3).

Apparently, the degree of involvement of the spinal neurones, of the subcortical nuclei and of the cortex in reactions to impulses from the inflammatory focus depends upon the activity of the inhibitory synapses. When they are blocked with strychnine a far greater number of neurones may become involved in the pathological reaction. Consequently the reaction may be so intense as to lose its adaptational significance.

LITERATURE CITED

1. Z. G. Biyasheva, Byull. éksper. biol., No. 3 (1964), p. 45.
2. L. N. Smolin, Transactions of the Institute of Normal and Pathological Physiology AMN SSSR, Moscow, 7 (1964), p. 86.
3. S. I. Frankshtein, Reflexes from pathologically altered organs, [in Russian], Moscow (1951).
4. P. Anderson, J. C. Eccles, I. Loyning et al., Nature, 200 (1963), p. 843.
5. K. Bradley, D. M. Easton, and J. C. Eccles, J. Physiol. (London), 122 (1953), p. 474.
6. J. S. Coombs, J. C. Eccles, and P. Fatt, Ibid 130 (1955), p. 374.
7. J. M. Crawford, D. R. Curtis, and P. E. Voorhoeve, et al., Nature, 200 (1963), p. 845.
8. D. R. Curtis, J. Physiol. (London), 145 (1959), p. 175.
9. J. Eccles, The physiology of nerve cells, [Russian translation], Moscow (1959).
10. J. C. Eccles, Ergebn. Physiol., 51 (1961), p. 299.

All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.
