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Tierexperimentelle Untersuchungen zum Elektrencephalogramm.

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The Development of Nerve Cell Rhythms.

By

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With 3 figures.

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The electro-physiologist of to-day with all his equipment of amplifiers and oscillographs must often reflect with humility on the achievements of his predecessors. GALVANI discovered animal electricity before the invention of the galvanometer, the action potential wave of muscle was analysed in detail by BERNSTEIN before any of the rapid recording systems had been made and WEDENSKY demonstrated the nature of the human electromyogram in 1884. With such examples from the past century we ought not to be so surprised at what was done by HANS BERGER in this. Yet it was surely a remarkable achievement to have established the nature and all the main features of the electroencephalogram with only a string galvanometer to record it. Only those veterans who have had to use this instrument near the limit of its sensitivity will appreciate the difficulties which must have faced him, but in spite of them he covered the ground so thoroughly that later work except in the clinical field has added remarkably little. Certainly it is never safe to claim any observation on the electroencephalogram as original until a careful study has shown that it is not already recorded in one of BERGERs papers.

Though BERGER paid great attention to the clinical abnormalities of the electroencephalogram he was constantly aware of the need for a better understanding of the normal. Here we have progressed very slowly. It would be optimistic to expect a complete explanation of the cerebral rhythms in terms of neurone activity, but it is disappointing to have so little that we can be sure of. In particular there is considerable uncertainty about the most striking feature of the electroencephalogram record, namely the disappearance of the α-rhythm when attention is aroused. BERGER regarded this as due to widespread inhibition of the cortex accompanying activity in a limited region. ADRIAN and MATTHEWS (1934) suggested that the disapparance of

the α waves might be due not to inhibition but to desynchronisation of the neurones with the consequent breakdown of the unified rhythm. It would be a simple matter to decide if we could record the activity of the individual neurones which are responsible for the α waves, but it is only in the projection areas that micro-electrode techniques give a clear record of axon discharges. In the association areas the axon spikes are very seldom large enough and it is in the association areas that the α-rhythm is most fully developed.

Yet we can learn something from the behaviour of the projection areas, particularly if they are studied over a wide range of anaesthesia. As BREMER has shown, the usual effect of the barbiturates is to produce a state in which the cortical neurones though still rhythmically active are very little influenced by afferent discharges. In very deep anaesthesia, however, when the rhythmical activity is reduced to no more than an occasional wave or short group of waves, it can be seen that an afferent discharge does produce some increase in activity though the effect is readily fastigued. In the somatic receiving area of the cat, for instance, a touch on the appropriate part of the body will often set up a short series of waves resembling those which occur from time to time without stimulation. Under lighter anaesthesia when the cortex is in continous activity the effect of an afferent discharge becomes much less obvious, but the dissociation between afferent fibres and cortical neurones becomes less and less as the anaesthetic wears off and when the animal is fully awake the cortical neurones can be more directly controlled. A continuous afferent discharge will now give a rapid succession of waves at a frequency of 50 a second and rhythmic touches will produce a corresponding rhythm in the cortex. Without afferent stimulation there is often a regular series of waves at 6—10 a second, comparable to the waves under deeper anaestesia, or to the α-rhythm, and these give place to the rapid 50 a second rhythm if the cortex is roused by a strong afferent discharge, or to small irregular oscillations if the afferent stimulus is less intense (fig. 1 A).

In the sensory receiving area, therefore, an afferent discharge has a facilitatory effect on cortical neurones deeply anaesthetised with a barbiturate, and on the unanaesthetised cells it gives a rapid rhythm, or else irregular small waves, in place of the slower rhythm at 10 a second. Here at all events there cannot be much doubt that the disappearance of the slow rhythm goes hand in hand with an increased activity of the cells, at all events of those which are directly influenced by the afferent discharge.

It is interesting to find the same sequence of events in the olfactory bulb. This has a structure which differs considerably from that of the cerebral cortex yet its electrical reactions are so much like

those of the cortical receiving areas that we must suppose them to depend on the general properties of nerve cell aggregates rather than on any particular structural arrangements.

The rabbit's olfactory bulb is easily reached through a small opening in the skull and a fine wire electrode can be fixed so that the uninsulated tip is in contact with one or other of the different layers. The outer layers are composed of the fine olfactory nerve fibres and of the glomeruli in which they arborise with the dendrites of the mitral cells. In the outer layers the only electric changes which can be recorded are oscillations of the sinusoidal type characteristic of grey matter

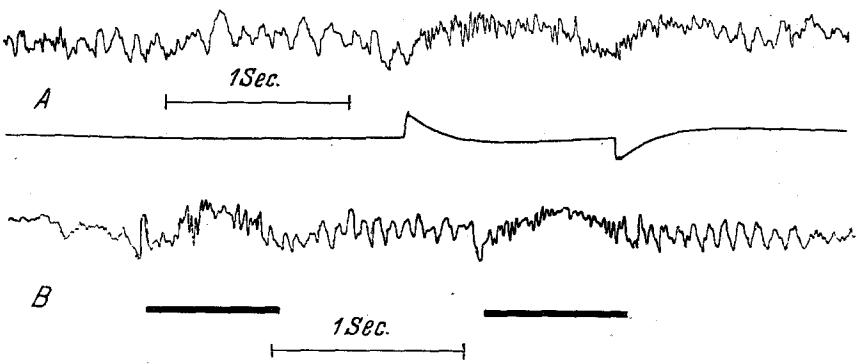

Fig. 1A and B. A Potential oscillations from the cerebral cortex of a cat after ether anaesthesia. The record is from the sensory receiving area for the forelimb and shows the change from slow to rapid waves when the foot is touched. B From the olfactory bulb of a rabbit under Nembutal. Olfactory stimulation by Eucalyptus at each period of inspiration (marked by horizontal line). Rapid irregular waves during stimulation followed by slow rhythm.

in general. With the electrode inserted more deeply axon potentials begin to appear and when the tip is in the layer of fibres which go to form the olfactory tract the potential spikes are the most prominent feature of the record. The discharges in these fibres can be compared with those in the optic nerve in that both are derived from neurones which have synaptic but not direct connection with the receptor endings.

The primary object of the work has been to study the way in which the olfactory organ detects and discriminates smells. For this it is best to use a preparation so deeply anaesthetised that the sinusoidal oscillations of the grey matter are suppressed, leaving only the response of axons. It is found that in some of these the connection with the receptors must be direct enough to be very little affected by the anaesthetic, for even in the deepest anaesthesia it is possible to detect a discharge due to an olfactory stimulus. In fact a small proportion of the olfactory tract fibres seem to respond in much the same way at all depths of anaesthesia, but the majority do not. The

majority remain inactive until the anaesthesia lightens and sinusoidal waves begin to appear from the grey matter. Then many axons are found to be giving a constant succession of potential spikes, often at a high frequency, and their continued activity may completely mask the presence of an olfactory discharge. But, as in the cerebral cortex, as soon as the animal has recovered completely from the anaesthetic this continous independent activity gives place to one which is intermittent and is controlled by the sensory stimuli. The olfactory discharge, now in a large number of fibres instead of only a few, can be detected at each inspiration: during expiration, or in the absence of a smell, some neurones remain in continuous activity but the majority are quiet.

The independent activity of the grey matter in light anaesthesia and the resumption of afferent control after recovery recalls at once what happens in the receiving areas of the cortex, for here too it is only in very deep anaesthesia that the independent activity is abolished and only after full recovery that the cortical waves are clearly related to the afferent signals.

As in the cortex, the waves developed by the grey matter of the olfactory bulb vary widely in frequency with the depth of the anaesthetic. Those produced by a strong olfactory stimulus seem to be due to structures beating synchronously at the highest frequency of which they are capable and this may vary from below 10 a second under very deep dial anaesthesia up to 60 a second in the unanaesthetised animal. But with moderate doses of dial or nembutal a stage is often found where in addition to the rapid rhythms produced by intense stimuli there are waves at a low frequency filling the intervals between the periods of stimulation. The record in fig. 1B illustrates the change from the slow rhythm to the small irregular oscillations produced by an olfactory stimulus of moderate intensity. Its resemblance to that from the sensory cortex of the cat (fig. 1A) needs no comment. The development of the slow rhythm can be followed in fig. 2. The depth of anaesthesia was enough to make all spontaneous activity die away if the olfactory organ was left unstimulated for a few minutes. Repeated olfactory discharges (produced by breathing air smelling of eucalyptus) raise the level of activity so that the cells begin to beat slowly during the periods between each inspiration. Immediately after the olfactory stimulus the rhythm is uncertain and the waves are small, but they increase in size and regularity until the rhythm is broken by the next period of stimulation. At each inspiration the stimulation of the olfactory organ produces an irregular series of potential spikes and this irregular activity disorganises the slow rhythm; but it can be seen that it does so by exciting rather than inhibiting, for at its reappearance the rhythm is faster than it becomes when fully

developed. When the smell is withdrawn and the stimulus very feeble the olfactory discharge may not be enough to appear in the record and then the only evidence of its occurrence is the disorganisation of the slow rhythm (fig. 2, *4*).

Records like these, showing the failure of the slow rhythm at each period of olfactory stimulation, recall immediately the electroencephalogram records from man showing the failure of the α-rhythm at each period of visual attention. They recall too the failure of the slow rhythm in the optic ganglion of Dytiscus when the eye is stimulated (ADRIAN, 1937). In fact the olfactory bulb gives us another

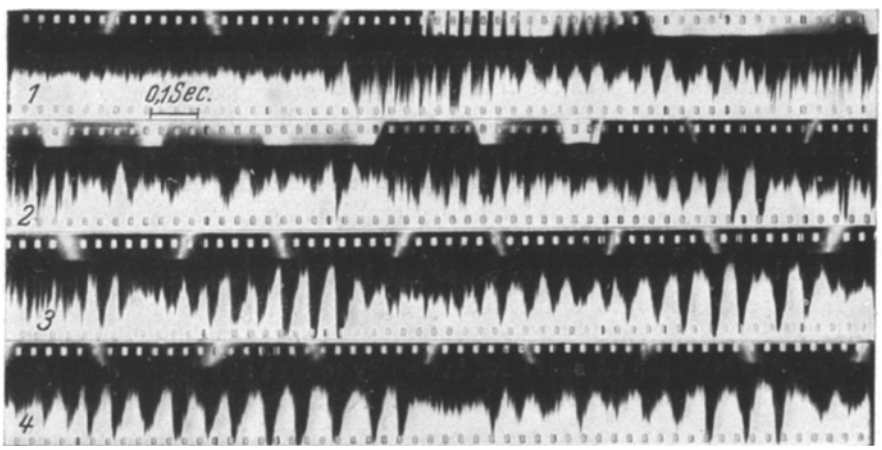

Fig. 2. Olfactory bulb of rabbit under nembutal. Consecutive records showing development of slow rhythm as the result of olfactory stimulation (by Eucalyptus). Periods of inspiration occur in the middle of each record: exposure to smell during records 1 & 2 marked by signal above. The slow waves are started by the sensory discharge, but the rhythm is disorganised by each period of stimulation.

example of the breakdown of a nerve cell rhythm as the result of a sensory stimulus.

In the records in fig. 2 the depth of anaesthesia was enough to make the slow rhythm die away if the level of activity of the bulb was not maintained by repeated olfactory discharges. The importance of afferent discharges in maintaining the general level of neurone activity has been clearly demonstrated by BREMER. In his encéphale isolé preparation of the cat, for instance, the section of the visual tracts leads to a great reduction in the slow wave activity of the cortex (BREMER, 1944). A further example from yet another nervous structure is shown in the records in fig. 3. These are from the optic nerve of the toad (Bufo vulgaris) when the eye is exposed to recurrent flashes of light. Initially, with the eye in darkness the retinal neurones are at rest, as are the neurones of the olfactory bulb in fig. 2. At each flash of light there is a large potential wave due to the primary nerve

discharge and this is followed, after an interval which becomes shorter and shorter with each stimulus, by a rhythmic after discharge at a rate of 16 a second. Each new period of stimulation disorganises the rhythm and it is reformed progressively as in the olfactory bulb. The chief difference is that in this case there is less tendency to continued activity for although there is no anaesthetic the waves soon die away and repeated stimulation is needed to maintain them.

The slow rhythm in the olfactory bulb, like that from the toad's retina, usually starts as the after effect of a stimulus and is appreciably faster when it is first reformed after a period of disorganisation. There is therefore a prima facie case for supposing that the stimulus has an excitatory rather than an inhibitory effect on the neurones of the bulb. But although this evidence favours desynchronisation rather than direct inhibition as the immediate cause of the breakdown of the waves, there is a further possibility which must be taken into account. In the olfactory bulb, as in the cortex, we are dealing with a preparation in which there are a great many nerve cells which are not on the direct pathway between the entering and leaving nerve fibres. It is probable that most of these cells can influence their immediate neighbours but that some of them would not be close enough to the main pathways to be much influenced by signals coming in from outside. Under moderate nembutal anaesthesia the excitability is depressed enough to keep the cells inactive but ready to beat at a low frequency if a small facilitating influence is added. For those which are near the main pathways a period of afferent stimulation will provide the necessary facilitation: these cells will start beating and as each provokes its neighbours the rhythm will spread more and more widely, the waves will become more regular and will grow in size as they do in fig. 2. Now it is not at all unlikely that the influence of the active cells will become greater and greater as their number increases, i. e. that the larger the number of cells beating in unison the greater the chance that the rhythm will spread to the outlying inactive groups. A large number of cells beating in unison would give simultaneous activity in many dendrites and there would also be larger potential changes or higher concentrations of humoral excitants than a few cells would give because the effect of the few would be more reduced by short circuiting or diffusion. BREMERS investigations of the strychnine waves in the spinal cord (BREMER, 1940) suggest that direct electric factors may be more important than dendritic conduction, but at all events whenever we find large regular potential waves developed by sheets or masses of nerve cells, it is reasonable to suppose that a certain proportion of the cells will have joined in the beat only because they are forced to do so by the massive effect of the rest. If so it follows that any disturbance of the rhythm (as by a renewed afferent stimulus)

would reduce the forces which constrain these cells to beat. They would become inactive, not from direct inhibition but because there was no longer a sufficient mass of cells, beating in unison, to keep them active. There is evidence from the olfactory bulb to support this suggestion, for it is found that an olfactory stimulus may cause either an increase or a reduction in the discharge of impulses from the neurones which are not on the direct pathway from the receptors. If these neurones have been reduced to complete inactivity by deep anaesthesia an olfactory stimulus may rouse them to activity again. This may die out after a few seconds or minutes if the stimulus is

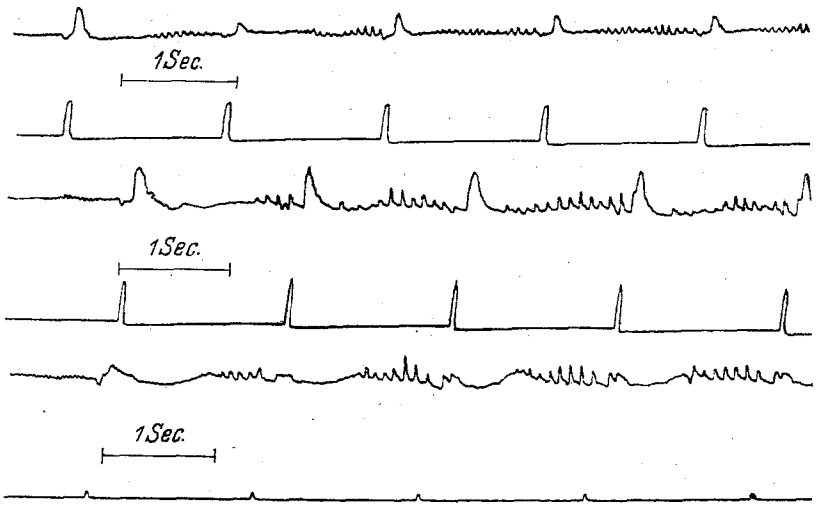

Fig. 3. Records from the optic nerve of the Toad (Bufo) showing the development of a rhythmic discharge by repeated exposure of the eye to a brief flash of light. Each flash disorganises the rhythm (Compare with fig. 2).

not renewed and it is increased temporarily at each period of stimulation. But in lighter anaesthesia when the neurones have reached the stage of persistent rapid activity an afferent discharge may have the reverse effect. Often it has none until the effects of the anaesthetic have almost worn off but ultimately a stage may be reached in which olfactory stimulation causes a marked reduction in the persistent discharge. Instead of a constant succession of axon spikes at a high frequency there is the large olfactory discharge at each inspiration with only scattered groups of impulses during the expiratory period. Here the afferent discharge certainly causes a suppression of activity. It is true that the activity which is suppressed is one of relatively high frequency: it is associated with a wave rhythm between 60 and 80 a second, which implies maximal rather than minimal excitation in the neurones. Presumably the olfactory discharge breaks up the rhythm by imposing its own lower frequency (about 50 a sec) on the

more accessible neurones so that those which were the pace-makers for the high rhythm have no longer a clear field in which to spread their effect. But clearly a low frequency rhythm might be suppressed in the same way, many of the neurones being reduced to inactivity by the disorganisation of the synchronised beat.

May not the α-rythm in the association areas depend on a similar mass effect? We are dealing here with a more complex system, no doubt, and the rhythm may be initiated by cells in some other region than the cortex, but it is quite possible that a number of the cells which take part in the rhythm would remain inactive if they were not forced to beat by the massive stimulus due to the cells already beating. The disorganisation of the rhythm would then lead to inactivity in some cells though others might be more active than before. Whether such a reduction to inactivity by a withdrawal of the stimulus should be classed as inhibition is a matter of definition, for it is scarcely comparable to the peripheral inhibitions where there is a definite reduction in excitability.

It is worth considering whether cumulative mass effects of this kind may not govern many of the fluctuations in activity in the brain. There is a possible example in the rapid spread of an epileptiform discharge over the cortex — „Nascitur exiguus, viresque acquirit eundo". It is true that synchronised beating tends to occur mainly at one or other end of the frequency scale, when the units are all intensely excited or when the exitation is near threshold value. For this reason it may not be a factor of much importance in regions which are in moderate activity. But the large sheets of nerve cells which form the silent areas of the cortex would be fertile ground for the development of such mass effects: it is at least possible that the function of these areas may depend in part on the number of cells in them which can be drawn into line with their neighbours to form relatively stable units.

Summary.

In the olfactory bulb of the rabbit under nembutal there are usually many neurones in a state of continous activity. These are very little influenced by olfactory stimulation and it is only when the anaesthesia has worn off that their independent activity gives place to one which is fully controlled by afferent signals. In deep anaesthesia however it can be seen that an afferent signal does produce an excitatory effect. At each olfactory stimulus there is the usual impulse discharge in some of the neurones and this is often followed hy a rhythmic succession of potential waves in the bulb. The renewed olfactory discharge at each inspiration disorganises the wave rhythm and it reforms progressively during the period of expiration. Records from the optic nerve

of the toad provide a further illustration of the formation and breakdown of a rhythm.

In these examples the primary effect of the discharge is excitatory and the disappearance of the waves is probably caused in the first instance by desynchronisation. But many of the neurones taking part in the rhythm may have been activitated by the large mass of cells already beating in unison. In such neurones the disorganisation of the beat will lead to a fall in activity. The failure of the α-waves in the association areas may be associated in the same way with a reduction in activity in neurones no longer stimulated by a massive rhythm. It is suggested that some of the properties of the cerebral cortex may depend on the mass effects which can be developed in large sheets of nerve cells.

Deutsche Zusammenfassung.

Im Bulbus olfactorius des Kaninchens unter Nembutalnarkose befinden sich viele Neurone in einem dauernden Aktivitätszustand. Dieser wird gewöhnlich durch Olfactoriusreize sehr wenig beeinflußt; erst nach Abklingen der Narkose wird die Eigentätigkeit durch eine andere Aktivitätsform ersetzt, die von afferenten Reizen abhängig ist. Doch kann in tiefer Narkose ein afferenter Reiz auch erregend wirken: Jeder Olfactoriusreiz macht zunächst die übliche Impulsentladung einiger Neurone und oft folgt hierauf eine rhythmische Folge von Potentialschwankungen im Bulbus. Die bei jeder Inspiration wiederkehrende Olfactoriusentladung stört (desorganisiert) den Wellenrhythmus, der sich allmählich während der Expiration wieder aufbaut. Ableitungen vom Nervus opticus bei der Kröte liefern ein weiteres Beispiel für den Aufbau und Zusammenbruch eines Rhythmus.

In diesen Beispielen ist die Hauptwirkung der Entladung excitatorisch, und das Verschwinden der Wellen wird wahrscheinlich in erster Linie durch Desynchronisierung verursacht. Doch werden viele am Rhythmus teilnehmende Neurone offenbar auch durch die große Anzahl von Zellen aktiviert, die bereits im gleichen Rhythmus entladen. In solchen Neuronen wird die Desorganisation des Rhythmus zu einem Absinken der Aktivität führen. Das Verschwinden der α-Wellen des EEG in den Assoziationsfeldern kann ebenso Begleiterscheinung einer Aktivitätsminderung in Neuronen sein, die nicht mehr länger durch einen Massenrhythmus angeregt werden. Es wird angenommen, daß einige Eigenschaften der Hirnrinde auf Massenwirkungen beruhen können, die sich in ausgedehnten Nervenzellschichten entwickeln.

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