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STUDIES ON THE EFFECTS OF DRUGS ON THE ELECTRICAL ACTIVITY OF THE BRAIN AND ON BEHAVIOUR*

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The experiments which I should like to describe this evening represent part of a study which my colleagues Dr. Hance, Mr. Key and I have carried out during the last few years, with the aim of trying to determine the sites of action of certain drugs in the brain. We were interested in those drugs which are known to have effects on mental function and, in particular, some which are used in psychiatry. None of these can really be classed as addiction drugs, but I think that the methods that have been used could be applied to the study of other drugs and therefore may be of interest to the members of this Society.

Our method has been to study the effects of a variety of drugs, together with certain combinations, on the electrical activity of the brain and on behaviour in four main types of animal preparation:

1. The intact conscious animal carrying permanently implanted electrodes in which behaviour and the EEG can be recorded simultaneously.

2. Animal preparations anæsthetized with barbiturates.

3. Two acute preparations, the *encéphale isolé* in which a section is made at the spinal level and the *cerveau isolé* in which the midbrain is transected. We have also studied the effects of drugs on arousal responses produced by stimulation of the brain stem and also by afferent stimulation, and I shall refer to these later on. For these experiments both cats and monkeys have been utilized. Of the many drugs studied I shall take physostigmine or eserine as an example of a parasympathomimetic drug, atropine as an anticholinergic drug, amphetamine as a central stimulant, *d*-lysergic acid diethylamide or LSD 25 as a hallucinogenic, chlorpromazine as a tranquillizer and pentobarbitone as a sedative.

First, a word as to the technique used for preparing chronic

* Given to the Society for the Study of Addiction on October 15th, 1957, in the rooms of the Medical Society of London, The President, Dr. W. R. Bett being in the Chair.

animal preparations with implanted electrodes and for this purpose cats have been utilized exclusively.(1) The electrodes, both for recording from different areas of the cortex and also for recording from the deeper structures of the brain, are screwed into the skull in an aseptic operation carried out under pentobarbitone anæsthesia. The leads from these electrodes are flexible and are taken down the back of the neck under the skin and brought out through the skin in the shoulder region in pairs. These leads are then attached to a small electrical socket, which in turn is carried in a leather harness which the animal retains permanently on its back. The harness is so designed as to allow freedom of movement in the animals, and it protects the area of skin through which the leads emerge and also takes any pull which may occur when the animal is connected up to the recording apparatus (see Bradley and Elkes, 1953, Figs. 8-10). It enables recordings of the electrical activity of the brain to be taken from the chronic preparations at will, simply by plugging a lead into the socket and connecting this to the EEG machine. A number of these preparations is kept in a communal animal house. For each experiment the animal is placed in a constant environment chamber, the purpose of which is to provide as far as possible a uniform environment so that the variable we are studying is the drug being used. The animal is then allowed a period of acclimatization before the experiment is started and we observe its behaviour and also take a control recording of the EEG. After this the drug is given and at suitable intervals we again record the EEG, and examine the behaviour.

In the normal conscious cat, before any drugs have been given, we find different types of EEG activity according to the behavioural state of the animal.(2) Thus, when the animal is drowsy or sleeping we see mainly large amplitude slow waves in the EEG and this disappears when the animal is awakened by a suitable stimulus (see Bradley and Hance, 1957, Fig. 1). At the same time the behaviour changes and the animal becomes more alert and more attentive to the environment. The EEG changes from slow wave activity to low amplitude fast activity which we associate with the alert state. This is known as the arousal response. Sometimes we see the development of an intermediate type of electrical pattern consisting of rhythmic activity, which we associate with an intermediate behavioural state and which we have called the "quiet" state. In all our experiments before any drugs were given it was found that the pattern of electrical activity observed correlated with the behavioural state of the animal.

When we injected a drug such as physostigmine in these animals in quite small doses (0·05-0·1 mg./kg.), we saw that the pattern of electrical activity of the brain changed to one similar to that seen in the alert animal, but in fact, the animal was not alert behaviourally and was often drowsy or quiet (see Bradley and Elkes, 1957, Fig. 28). Atropine on the other hand, in doses of 2·0-3·0 mg./kg., induced an electrical pattern of slow waves similar to those seen in sleep but here again sleep was not observed and the animal was in some cases slightly excited (see Bradley and Elkes, 1957, Fig. 2c). An arousal stimulus applied after atropine had been administered produced the usual behavioural change but no change in the electrical activity of the brain. Thus, when these two drugs are administered the correlation between behaviour and the EEG, which we normally see in these animals, was lost and we have a pharmacological agent producing a sleep type of record, and another producing an alert type of activity but without alerting corresponding behaviour.

When we used amphetamine, the effects on the electrical activity of the brain correlated with those on behaviour. With amphetamine in doses of 2-5 mg./kg., the animals became excited or hyperactive, whilst the electrical activity of the brain changed to the alert type of pattern (see Bradley and Elkes, 1957, Fig. 11) and somewhat similar effects were observed with LSD 25 (15-30 μg./kg.). With these two drugs therefore, the changes in electrical activity of the brain and in behaviour were still correlated with each other. There were however, some differences between their effects. Whereas amphetamine produced an alerting which was independent of the environmental conditions, in the case of LSD 25 the degree of alerting depended upon whether the animal was in a quiet or noisy environment and when all environmental stimuli had been rigidly excluded, the degree of alerting produced by this drug was correspondingly less. When we used atropine in combination with either amphetamine or LSD 25, it was found that the animal remained excited and alert, but that atropine still produced its characteristic pattern of slow waves. This suggests that the behavioural effects of amphetamine and LSD 25 predominate but that the electrical effects of atropine are dominant.(2)

Chlorpromazine was found to induce a state of drowsiness and indifference, both to the environment and to the observer, in animals which had previously been friendly and affectionate.(3) The animals became less active and their EEG reflected these behavioural changes by showing more slow activity (see Bradley and Hance, 1957, Fig. 2). No response, either behavioural, or in terms of the

electrical activity of the brain, could be produced by the usual alerting stimuli after the drug had been given, although painful stimuli still produced some response. When used in combination with the other four drugs, chlorpromazine was found to block both the behavioural and the EGG effects of amphetamine and LSD 25, irrespective of the order in which the drugs were given. Physostigmine and atropine, on the other hand, both produced their own characteristic changes in electrical activity when given after chlorpromazine. Thus, physostigmine produced an EEG record of low amplitude, fast activity whilst the animal remained drowsy and indifferent, and atropine induced slow waves, but without making the animal any more drowsy.

In the acute preparations, the *encéphale isolé* and the *cerveau isolé*, we see different types of electrical pattern. In the *encéphale isolé*, in which the spinal cord is sectioned at the C1 level, there are two main patterns of electrical activity, one which is normally associated with drowsiness and one which is associated with alertness, and we can change the drowsy pattern to the alert pattern by the application of suitable sensory stimuli to the head. Moreover, this preparation can still be roused from the drowsy state. On the other hand the *cerveau isolé*, in which the mid-brain is transected, is permanently asleep; it no longer responds to sensory stimuli and shows an EEG record of slow waves characteristic of sleep. In these preparations we were able to observe simultaneously the effects of drugs both on the electrical activity of the brain and on blood pressure.(2) Physostigmine and atropine were found to produce similar changes in the electrical activity of the brain in the acute preparations to those which were observed with these drugs in the conscious animal. That is to say, physostigmine produced pattern of low amplitude, fast activity similar to that of the alert animal and atropine produced a pattern of high amplitude, slow waves similar to those seen in sleep and these effects appeared in both of the acute preparations, i.e. both after spinal section and after mid-brain section (see Bradley and Elkes, 1957, Fig. 9). It was also observed in these experiments that the injection of small quantities of acetylcholine produced an effect similar to that caused by physostigmine but that this effect was much more transient. It is therefore possible that those effects of physostigmine, which had been observed in other experiments with this drug, might have been due to its known anticholinesterase action, which allowed the accumulation of acetylcholine to take place.

Amphetamine was also used with the acute preparations and this

drug was found to have effects in the *encéphale isolé* which were similar to those seen in the conscious animal, i.e. alerting of electrical activity and also of behaviour, as far as behaviour can be examined in this preparation. This drug had no effect in the *cerveau isolé* and its effects on the electrical activity of the brain therefore appeared to be abolished by transection of the mid-brain. LSD 25 on the other hand, had no effect on either of the acute preparations and thus its effect on the electrical activity of the brain appeared to be abolished by transection of the spinal cord. Chlorpromazine, like amphetamine, produced effects on the *encéphale isolé* which were similar to those observed in the conscious animal, but this drug also had no effect on the *cerveau isolé*.(3)

At the time these experiments were being carried out, Moruzzi and Magoun(4) had just published their findings on the arousal system of the brain and it seemed that our own results were related to theirs. They had found that electrical stimulation of parts of the reticular formation of the brain stem, together with certain parts of the mid-brain tegmentum produced changes in the electrical activity of the cortex which were widespread and which were similar to those seen in arousal. They also found that lesions in this system, the reticular formation, not only blocked these effects, but when carried out in chronic preparations produced permanent somnolence from which the animal could no longer be roused by sensory stimuli. On the other hand, lesions confined to the lateral pathways, including the lemniscal systems did not produce somnolence.(5) Thus, it appeared that only lesions confined to the medial parts of the brain stem, which the authors claimed did not interfere with conduction in the afferent pathways, produced somnolence. There is of course some clinical evidence that injury to the brain stem can produce loss of consciousness and coma. Magoun and Moruzzi postulated the existence in the brain stem of an arousal system, the Brain Stem Reticular Activating System which, through diffuse ascending pathways, influences the entire cerebral cortex. This system in turn receives impulses via the collaterals feeding into it from the afferent pathways.(6) There is now a considerable volume of data to support this hypothesis and also evidence for the existence of these collaterals. It has also been found that afferent impulses reaching the reticular formation lose their identity and produce diffuse effects.

The levels of section in our acute preparations may be correlated with the influence of this reticular system on the cortex. Thus, the spinal section should have little effect on the arousal system and its ascending influence, but the mid-brain section will cut off the influ-

ence of the brain stem reticular activating system and this presumably accounts for the fact that the preparation with this transection is permanently asleep. It is therefore possible to correlate the results of our experiments with these findings and to suggest possible sites of action for some of the drugs (Fig. 1). Since amphetamine and

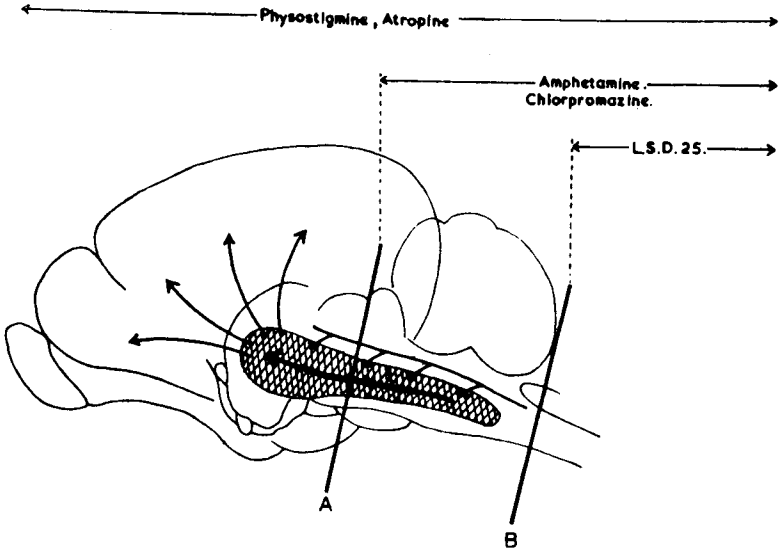


FIG. 1

Diagram of the cat brain showing the reticular activating system of the brain stem and its ascending influence to the cortex, together with the planes of section of the acute preparations, A. for the *cerveau isolé* and B. for the *encéphale isolé*. The levels at which the effects of the various drugs were present, are also indicated.

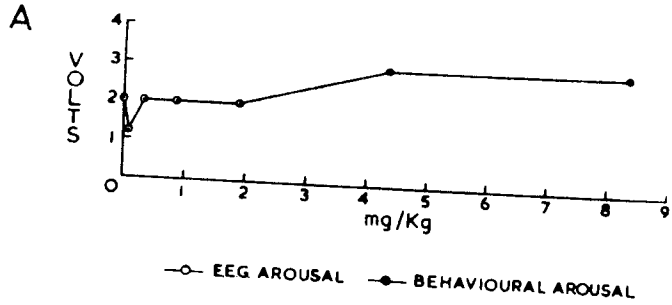
chlorpromazine produced effects in the acute preparations after section of the spinal cord, but had no effect after transection of the mid-brain, and since these two drugs produced in the conscious animal effects on electrical activity which correlated with behaviour, we may suggest that these two drugs probably act on receptors which are situated in the brain stem and these may be in the reticular activating system itself. (2 and 3) On the other hand, physostigmine and atropine, which produced effects on the electrical activity of the brain after transection of the mid-brain, were the drugs which, in the

conscious animal, produced electrical effects dissociated from behaviour and it might be thought that these drugs are in all probability not acting on the reticular activating system but perhaps have a more diffuse action, possibly on a system which is less concerned with changes in wakefulness and sleep. I shall return to this possibility a little later on. LSD 25, on the other hand, does not fit into either of these categories and appears to be in a position on its own. Further investigations have been carried out with this drug and the results of these will I think, throw further light on its possible site of action.

We thought at this stage that it would be interesting to study the effects of these drugs on arousal produced in the same way as that produced by Moruzzi and Magoun, namely by stimulation of the reticular formation, and this we have done in acute experiments, measuring the threshold at which both EEG and behavioural arousal were produced and then injecting the drug, after which we again checked the threshold to see if it had changed. In this way we were able to plot a graph of the arousal threshold for increasing quantities of the drugs and we found that these graphs are consistent for the same drug used in different experiments. In some experiments we also measured the threshold for arousal produced by afferent stimulation since this seemed to be relevant, and in these experiments we used auditory stimulation.(7)

Pentobarbitone was found to have a marked effect on arousal thresholds. Small doses of this drug caused the thresholds to rise rapidly and doses of the order of 10 mg./kg. blocked arousal completely (Fig. 2b). On the other hand chlorpromazine had a relatively small effect on arousal thresholds (Fig. 2a). The rise in threshold was slight even when large doses of chlorpromazine were used (up to 10 mg./kg.), so that there were marked differences between these two drugs in terms of their effects on arousal thresholds. Chlorpromazine was found to block arousal produced by afferent stimulation in relatively small doses, so that the effect of this drug in blocking afferent arousal might be considered to be more specific than that of barbiturates and it is possible that, whereas barbiturates probably have a direct depressant action on the reticular formation, chlorpromazine may have a depressant effect more closely related to the influence of the afferent collaterals entering the reticular formation at this level. We have, in fact, received some confirmatory evidence for this idea from recent experiments, in which we found that conduction in the reticular formation was blocked by barbiturates but not by chlorpromazine,(8) and in studies of the action of these drugs

on the activity of single neurones in the brain, chlorpromazine was found to modify responses of single units to afferent stimulation.(9)



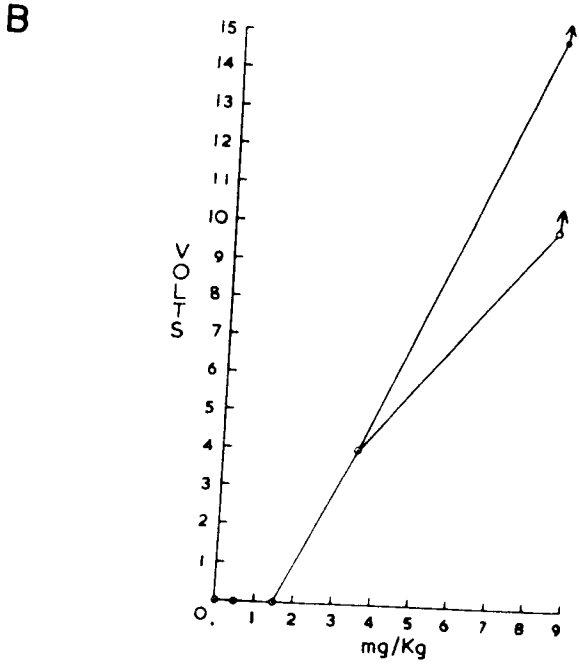


FIG. 2

Graphs showing the effects of varying doses of A. chlorpromazine and B. pentobarbitone on the threshold for arousal produced by electrical stimulation of the reticular formation of the brain.

In studies with atropine and physostigmine on arousal thresholds, we found that with these two drugs the graphs for behavioural and EEG arousal showed the greatest divergence (Fig. 3). Thus, the

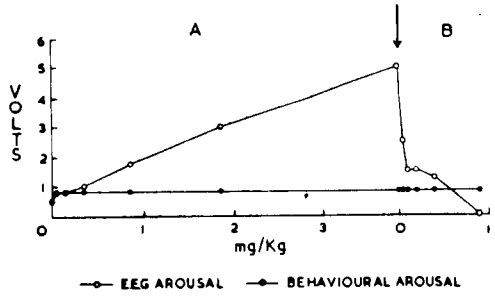


FIG. 3

Graphs showing the effect of atropine followed by physostigmine on the thresholds for behavioural and EEG arousal produced by stimulation of the reticular formation. The point of injection of physostigmine is indicated by the arrow.

threshold for EEG arousal rose steadily as we injected atropine, but the threshold for behavioural arousal did not change appreciably. When we followed atropine with physostigmine, the threshold for EEG arousal fell again, whilst the behavioural threshold still did not change. The results obtained in these experiments confirm the dissociation between the electrical and behavioural effects of these drugs and emphasize still further the possibility that they may be acting on a system which is less concerned with behaviour and only with changes in electrical activity, as far as arousal is concerned.

Amphetamine and LSD 25 were studied both in terms of their effects on arousal produced by stimulation of the reticular formation and also arousal produced by afferent (auditory) stimulation. Dealing first with arousal produced by stimulation of the reticular formation, we found that amphetamine produced a lowering of the arousal threshold when increasing doses were given, until eventually the preparation became permanently alert (Fig. 4a), whilst LSD 25 had no effect on this threshold. Now, if we turn to the arousal threshold for afferent stimulation, we find that amphetamine lowered the threshold at much the same rate as it lowered the threshold for stimulation of the reticular formation (Fig. 4b). LSD 25 also had a pronounced effect on the afferent arousal threshold, but this drug had no effect on the threshold for direct stimulation of the reticular

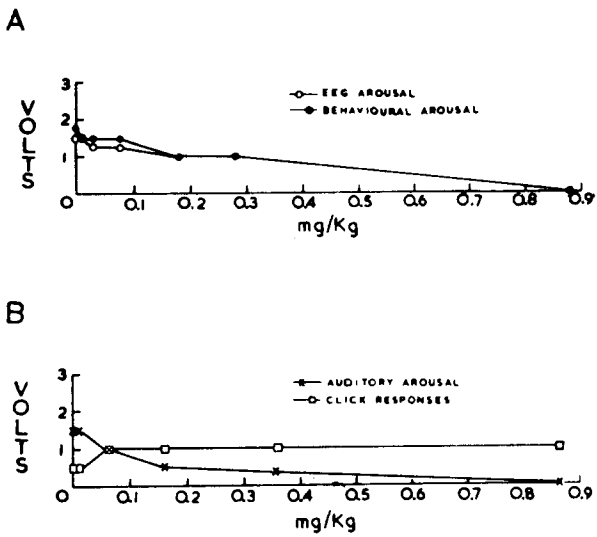


FIG. 4

Graphs showing the effect of amphetamine:— A. on the threshold for arousal produced by direct stimulation of the brain stem reticular formation and B. on the threshold for arousal produced by afferent (auditory) stimulation (crosses). The threshold for click responses recorded from the auditory cortex is also shown (open squares).

formation (Fig. 5). So that, whereas amphetamine appears to be acting directly on the reticular formation of the brain with, in this case, excitant action, LSD 25 appears to have no direct action but may have an action which is more closely related to the afferent input to this system. This drug seems to have an action which may in some way sensitize the reticular formation to the afferent input. This idea would be consistent with our observations in the conscious animal, where the effects of LSD 25 appeared to be dependent upon environmental conditions, whereas those of amphetamine were not. In these experiments it was found that neither amphetamine nor LSD 25 had any appreciable influence on the threshold for "click" responses recorded from the auditory cortex, suggesting that these drugs had little or no direct effect upon the afferent pathway itself.

Finally, I should like to summarize these findings into one hypothesis regarding the sites of action of these various drugs, and I would like to suggest that there are probably three different sites of

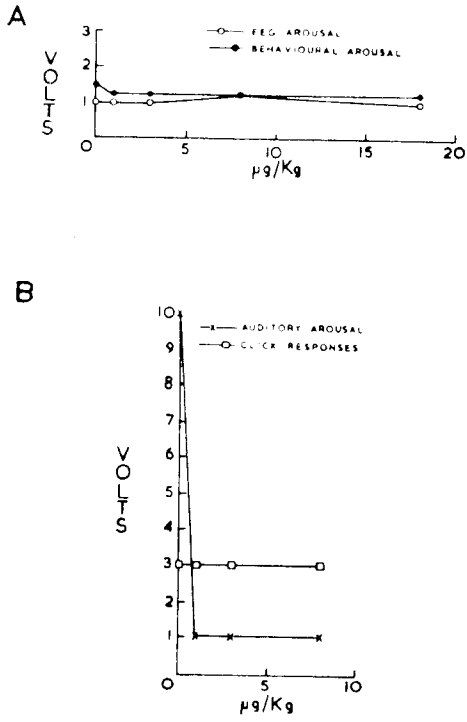


FIG. 5

Graphs showing the effect of LSD 25 A. on the threshold for arousal produced by direct stimulation of the brain stem reticular formation and B. on the threshold for arousal produced by afferent (auditory) stimulation (crosses). The arousal for click responses recorded from the auditory cortex is also shown (open squares).

action and possibly three types of receptor for these drugs in the central nervous system (Fig. 6). Firstly, we have those drugs which appear to have a direct action on the reticular formation of the brain; this may be either a depressant action, such as that of the barbiturates, or an excitant action, such as that of amphetamine. Secondly, we may have an action at the level of the brain stem, but which is apparently more closely related to the incoming influence of afferent collaterals entering the brain stem. This again may be a depressant action, such as that produced by chlorpromazine, or it may be excitant, such as that of LSD 25. Thirdly, we have an action

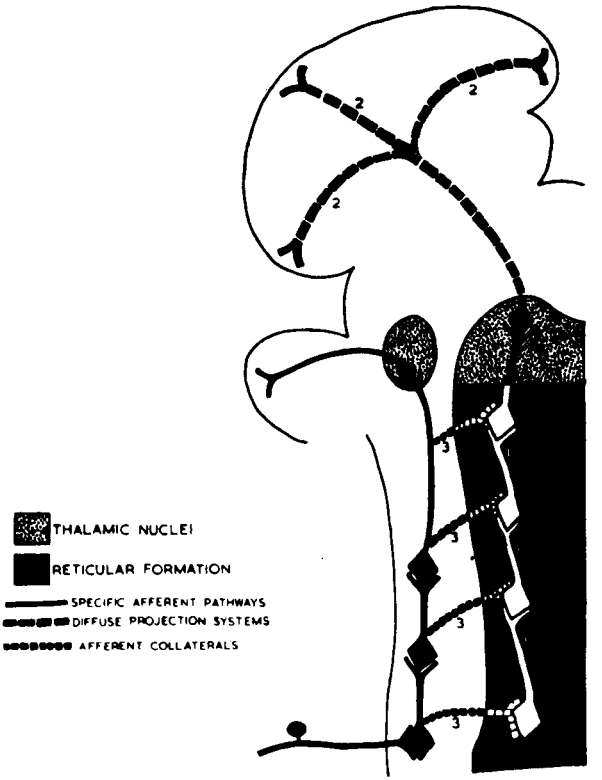


FIG. 6

Hypothetical diagram representing the specific and non-specific pathways to the cortex and showing the suggested sites of action for certain drugs: (1) the reticular formation, (2) the diffuse thalamic projection system and (3) the afferent collaterals entering the reticular formation.

(From P. B. Bradley, in "The Reticular Formation of the Brain". Little, Brown & Co., Boston, Mass. In press.)

on a system which produces diffuse cortical electrical effects but which is apparently not concerned with behavioural changes in terms of sleep and wakefulness. This is the action of physostigmine and atropine and it may possibly be on diffuse thalamic projection systems.

At the present time it is not possible to relate drug effects in animals to those in man, and we need more comparative studies

in different species before this can be attempted. However, the animal experiment can provide us with further evidence regarding the mode of action of drugs in the central nervous system and the crude hypothesis which I have outlined suggests that at least three different types of receptors for drugs exist in the brain. Whether or not these act through neurohumoral transmitter mechanisms we cannot say, and whilst this is an attractive hypothesis, the possibility of an action through an interference with enzyme systems or through local changes in vascular tone cannot be excluded.

REFERENCES

(1) Bradley, P. B. and Elkes, J., *Electroenceph. clin. Neurophysiol.* (1953), **5**, 451-456.
(2) Bradley, P. B. and Elkes, J., *Brain* (1957), **80**, 77-117.
(3) Bradley, P. B. and Hance, A. J., *Electroenceph. clin. Neurophysiol.* (1957), **9**, 191-215.
(4) Moruzzi, G. and Magoun, H. W., *Electroenceph. clin. Neurophysiol.* (1949), **1**, 455-473.
(5) Lindsley, D. B., Schreiner, L. H., Knowles, W. B. and Magoun, H. W., *Electroenceph. clin. Neurophysiol.* (1950), **2**, 483-498.
(6) Starzl, T. E., Taylor, C. W. and Magoun, H. W., *J. Neurophysiol.* (1951), **14**, 479-496.
(7) Bradley, P. B. and Key, B. J., *Electroenceph. clin. Neurophysiol.* In Press.
(8) Hance, A. J. Unpublished data.
(9) Bradley, P. B. and Magni, F. Unpublished data.