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ELECTROENCEPHALOGRAPHIC AND BEHAVIOURAL CORRELATES OF AN INSTRUMENTAL REWARD CONDITIONED RESPONSE IN RABBITS

A PHYSIOLOGICAL AND PHARMACOLOGICAL STUDY[1]

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Numerous electroencephalographic obser-ons during the process of conditioning and performance of conditioned responses have n made, mainly in cats, dogs, monkeys and n. Rabbits, on the other hand, have seldom n used in these investigations, although eral conditioning techniques have been cribed.

The present work was undertaken for two ons. The first goal was to investigate the G patterns associated with the rabbit's con-oned behaviour. The other aim was to apply his animal a method of simultaneous be-oural and EEG study for a pharmacological arch, in order to study the influence of ous drugs on the conditioned reflex and on electrical activity of the brain.

MATERIALS AND METHODS

The experiments were performed on eight t male rabbits, each weighing from 2–2.5 in which cortical and subcortical electrodes been implanted. The instrumental reward itioning described by Malinovskii (1952) abbits was used. The animal is taught, in er to obtain food, to pull a ring with its outh during the sound of a buzzer.

The training was carried out in a cage ipped with a ring and a feeding device e of eleven cups mounted on a turning el which allowed the food to be presented through a hole in the floor. The cage was in a sound-proof room, provided with a mirror system which allowed observation of the animal's behaviour. The electrodes were implanted either before or during the acquisition of the conditioned response, using a method described previously (Longo 1960). Briefly, four stainless steel electrodes were screwed into the skull at the level of the anterior sensorimotor and of the associative cortex. Subcortical concentric electrodes were also inserted and their anatomical location was ascertained histologically at the end of the experiments. The operation had no significant influence on the conditioned behaviour of the rabbit.

During the experiments the electrodes were connected to a Grass Model III D electroencephalograph by means of long flexible wires which did not hinder the free movements of the animal.

Elaboration of the conditioned response. The training procedure consisted of two stages. First, the learning of the ring pulling exercise and second, the learning of the specific conditioned response.

The animals were taught to pull the ring in order to obtain food from the feeding device. This response is learned quite readily when hints are provided during the training period. Good results were obtained when a piece of food was fixed to the ring in order to attract the animal's attention. Every time the animal bit the food attached to the ring, a piece of food was presented in the feeding cup. After a certain number of trials (50–100 given over a 4–7 day period, depending upon the animal), the exercise was performed without the food

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placed in the ring. From this time on the animal was kept on a daily diet of 70 g of oats and 100–150 g of grass or carrots. This food was given to the animal after the experiment and was eaten during the following 2–3 h. This amount of food, although it is sufficient to keep the animal's weight stable, does not satisfy completely the animal's food requirements. Thus the rabbit, placed in the training cage, is always eager to find food. The performance of the test depends on the kind of food used. Carrots, cabbage and clover were tested. The best results were obtained with cabbage, and for this reason, cabbage was used in the present experiments. When the trained rabbit was put into the cage, it ran immediately to the ring, pulled it and took the food from the feeding cup. This exercise was repeated 20–30 times. Then the intervals between the pullings became longer and longer, until finally the animal ceased to work for its food.

In the second stage of training an acoustical stimulus (the sound of a buzzer) was presented in order to teach the animal to pull the ring only when the buzzer was on. During the first trials the sound of the buzzer produced an orienting, sometimes fear, reaction. After several presentations, however, the animal became quite indifferent to the sound. At this point the specific conditioning procedure was started. The rabbit was then rewarded with food only when it pulled the ring during the sound of the buzzer. In the early sessions the pullings during the sound of the buzzer occurred accidentally. The rabbit, which did not find food after it had pulled the ring without the buzzer, became excited: it pulled many times with great violence and bit the ring. In the third or fourth session the initial signs of conditioning were observed, *i.e.*, the animal obviously began to respond to the buzzer, spontaneous pullings became less violent and less frequent and finally occurred only occasionally. When the animal was fully conditioned the buzzer was presented for 30 sec at intervals varying from 1–4 min. Once the rabbit had learned the exercise, it was possible to maintain this state by means of one to two sessions a week. This provided a trained animal which was used to assess the effects of various pharmacological agents. Even without intermittent training sessions, the rabbits retained the conditioned response over a period lasting more than 2 months.

The following drugs were used: scopolamine, eserine, chlorpromazine, imipramine, lysergic acid diethylamide and *d*-amphetamine. The drugs were dissolved in distilled water and injected into the marginal ear vein. All the doses are referred as the weight of free base. In some trials saline was administered in order to exclude a possible non-specific action of the injection on the conditioned response.

RESULTS

I. *Behavioural and EEG patterns during the instrumental reward conditioned response*

After the instrumental reward conditioned response (ICR) had been established, all the animals behaved alike. When it was put into the cage, the rabbit performed a few searching movements and then became quiet, but alert, until the conditioned stimulus (CS) was applied. Upon the sound of the buzzer it ran immediately to the ring, pulled it and took the cabbage from the feeding cup. After it had eaten, it usually moved to the far corner and awaited the next signal. The latency of the ICR was different in various stages of the experiments. In the first trials it varied between 2–6 sec, later it increased gradually up to 20 sec. After 20–30 positive responses the rabbit ceased to perform the exercise (Fig. 5*A*), remaining motionless or lying on the floor of the cage.

From the moment the animal was placed into the cage, an activated EEG tracing was registered. Low voltage 25–30 c/sec waves were present in the cortical leads, together with a regular 4–6 c/sec activity (theta rhythm) in the dorsal hippocampus. A mixed activity made up of 4–6 c/sec waves and 20–30 c/sec lower voltage waves was registered from the ventromedial nuclei of the thalamus. In about 25 per cent of the trials, rapid (60 c/sec) waves of an amplitude of 100–200 μV were recorded from the anterior sensorimotor cortex. At the sound of the buzzer there were, however, some modifications induced by the CS. In the majority of trials a change was observed only in the hippo-

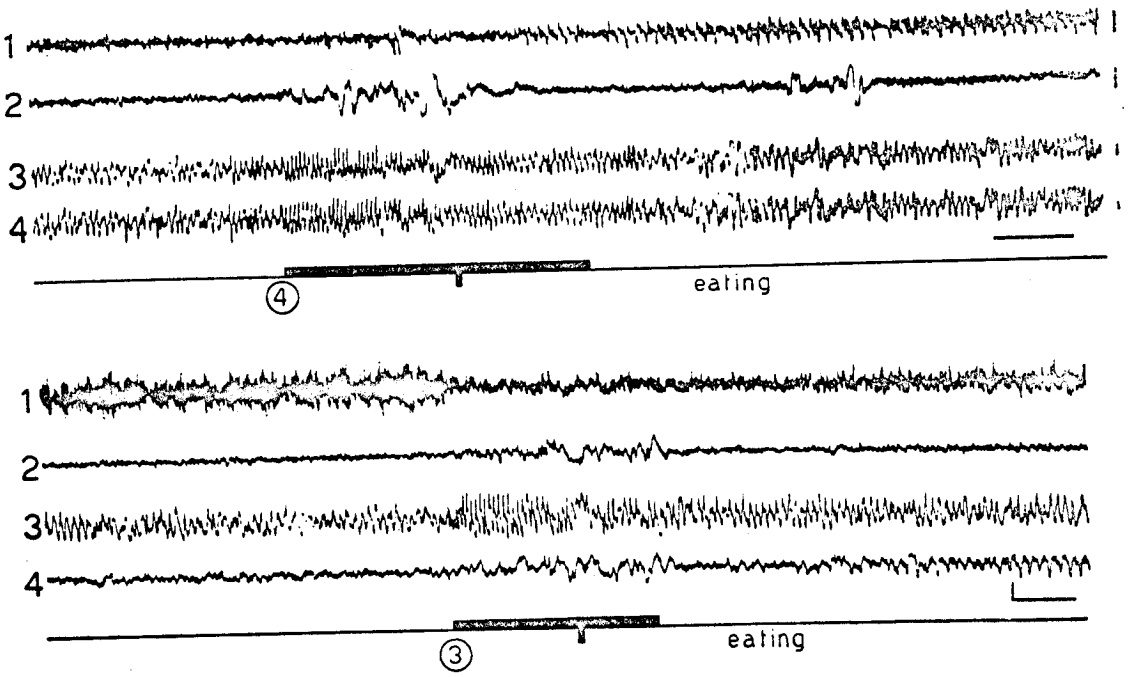

Fig. 1

Leads of the upper tracing: 1. anterior sensorimotor cortex; 2. associative cortex 3. left dorsal hippocampus; 4. right dorsal hippocampus. Calibration: 100 μV, 2 sec.

Leads of the lower tracing: 1. anterior sensorimotor cortex; 2. associative cortex, 3. left dorsal hippocampus; 4. right ventromedial nucleus of the thalamus. The horizontal black line indicates the duration of buzzer sounding. The number of the trial is indicated below the line. The vertical mark indicates the rabbit response of pulling the ring. Calibration: 200 μV, 2 sec.

The figure illustrates two different EEG patterns observed during the alimentary conditioned reflex. In the upper tracing there is an increase in voltage and in the frequency of the hippocampal waves when the conditioned stimulus was presented with no changes in the cortical leads. During the eating period "masticatory" waves appear in the anterior sensorimotor cortex. The lower tracing shows 60 c/sec high voltage waves in the anterior sensorimotor cortex (frequency measured in curves recorded at high speed), which disappear when the conditioned stimulus is presented. The modifications of the hippocampal recording are similar to those shown in the tracing reproduced above.

campal tracing (Fig. 2). The synchronous 4–6 c/sec waves slightly increased in voltage and frequency (up to 8–9 c/sec). In a few cases a change of the cortical tracing was also observed. This occurred when the 60 c/sec waves were recorded from the anterior sensorimotor cortex. When the buzzer sounded, the tracing from the anterior sensorimotor cortex changed to low voltage 25–35 c/sec waves (Fig. 1). These changes lasted only during the performance of the exercise. When the animal began to eat the food, the tracing returned to the patterns observed before the presentation of the CS, and rhythmic sharp waves of a voltage from 100–300 μV appeared first in the anterior sensorimotor cortex and then spread to other cortical and, less frequently, to subcortical leads. These waves, previously described and extensively studied by Ectors (1936) and by Longo (1960), are synchronous with the chewing movements. This characteristic pattern will be referred to in the present paper as "masticatory" waves, a term which is based on the translation of the French *ondes masticatrices* originally used by Ectors (1936). Sometimes, however, the "masticatory" waves failed to appear. Less often, during the eating period, the tracing from the sensorimotor cortex became synchronized

Fig. 2

Leads: 1. anterior sensorimotor cortex; 2. associative cortex; 3. left dorsal hippocampus; 4. right dorsal hippocampus. Calibration: 200 μV, 2 sec. EEG synchronization during the eating period. The "masticatory" waves (barely noticeable in lead 2 of the upper tracing) completely disappear with the onset of the synchronization. Note the abrupt desynchronization occurring at the end of the mastication. The lower tracing is the continuation of the upper one.

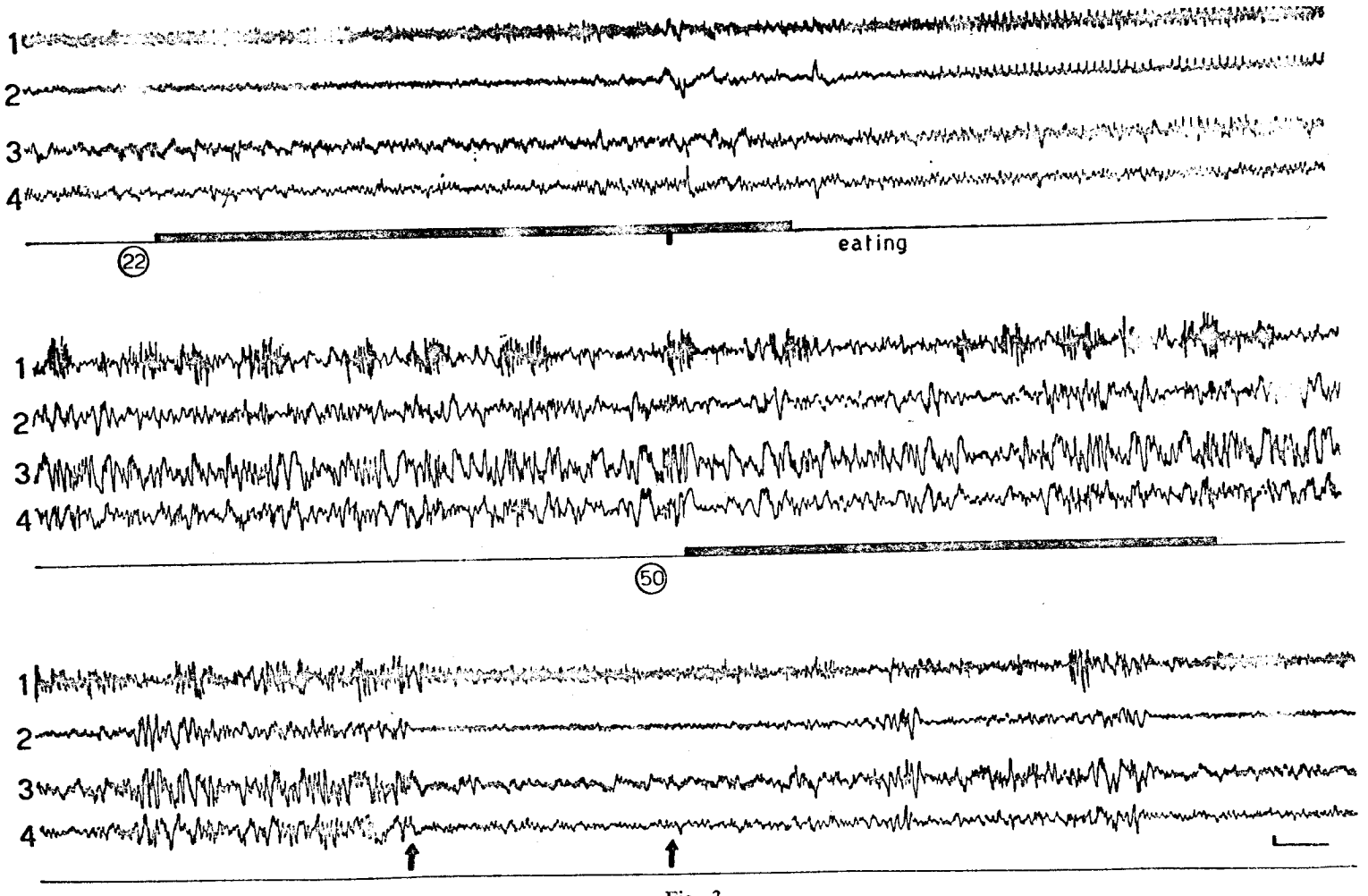

Fig. 3

Leads: 1. anterior sensorimotor cortex; 2. associative cortex; 3. left dorsomedial nucleus of the thalamus; 4. right ventromedial nucleus of the thalamus. Calibration: 100 μV, 2 sec. Changes in the EEG patterns during various stages of the ICR. Upper tracing: during the performance of the ICR the tracing is activated. Middle tracing: the rabbit ceases to respond to the conditioned stimulus; the tracing is synchronized and is not modified by the buzzer. Lower tracing: another stimulus (at the arrows: knocking at the window of the sound-proof room) evokes a desynchronization of the tracing.

and, also, when this happened, no "masticatory" waves were present (Fig. 2).

When the rabbit finished eating, the "masticatory" waves disappeared and a desynchronized tracing occurred as the animal moved to the far corner of the cage. This desynchronization was also observed when the eating period was characterized by a synchronized activity (Fig. 2).

After 20–30 trials, when the rabbit ceased to respond to the CS (period of satiation), high voltage 2–3 c/sec waves appeared in all leads, plus spindles in the anterior sensorimotor cortex. Further presentations of the CS did not produce any EEG changes. It is worth noting that an extra-stimulus (knocking at the window) given during this period could cause desynchronization of the EEG (Fig. 3). Subsequently, the next CS evoked some desynchronization. Further applications of the CS, however, failed to alter the electrical activity of the brain.

II. *Influence of drugs on the ICR and EEG activity*

Scopolamine and eserine. The effects of scopolamine and eserine were studied in 35 experiments performed on seven rabbits. In doses up to 0.05 mg/kg, scopolamine did not interfere with the ICR. After higher doses (0.1–0.3 mg/kg i.v.), spontaneous motor activity increased. When the buzzer sounded, the animal did not pull the ring, but performed instead purposeless movements around the cage. Occasionally the conditioned response was performed, but the pulling was less intense and occurred after a long latent period. In three out of the seven rabbits the increase in spontaneous activity was less evident, but the performance of the ICR was always disrupted. The animal, however, would eat food placed in the cage independently of the performance of the ICR.

From the EEG point of view, 0.05 mg/kg of scopolamine, although it did not influence the performance of the ICR, produced some modifications in the tracing. The 4–6 c/sec rhythm in the hippocampal lead became less evident, and 2–3 c/sec high voltage waves appeared in the cortical leads. In these instances the CS produced a slight activation of the tracing. During the eating period, however, the "masticatory" waves did not appear. With higher doses (0.1–0.3 mg/kg) the synchronizing effect was more pronounced. Spindles, intermingled with slow waves, appeared in the anterior cortical leads. No modifications of the tracing were observed during the CS (Fig. 4).

Eserine, in doses up to 0.15 mg/kg, exerted no influence on the ICR. Higher doses were followed by autonomic and motor disturbances, such as fasciculation, increase of muscular tone, salivation, urination, diarrhoea and polypnoea. Usually these effects appeared with doses of 0.2–0.25 mg/kg. In these instances no conditioned response occurred and the animals did not eat even when they were presented with food without the conditioning procedure. A continuous activation of the EEG was observed in animals treated with eserine.

When 0.1–0.2 mg/kg of eserine was administered to rabbits previously treated with scopolamine (0.1–0.2 mg/kg), the ICR was restored. This effect was fully demonstrated in six out of seven animals, in seven different experiments (Fig. 4 and 5). The return of the ICR was accompanied by the restitution of the activation patterns in the EEG.

Chlorpromazine was tested in thirteen experiments performed on three rabbits. Doses from 0.2–1 mg/kg i.v. had little influence on the ICR and the EEG tracing. The ICR could be blocked only after the administration of 2–3 mg/kg of the drug. With these doses motor depression and postural disturbance were observed. Sometimes, however, despite the marked impairment of the movements, the animal ataxically approached the ring when the buzzer sounded. The rabbits ate food placed into the cage independently of the performance of the ICR.

After high doses, synchronization of the EEG ensued, with spindles appearing in the anterior sensorimotor cortex. A shortly-lasting desynchronization accompanied the sound of the buzzer.

Amphetamine. The effect of amphetamine was studied in fifteen experiments performed on three rabbits. Doses ranging from 0.5–5 mg/kg were injected. The effects of this drug on the ICR varied according to the dose employed. Doses of 0.5–2 mg/kg caused the per-

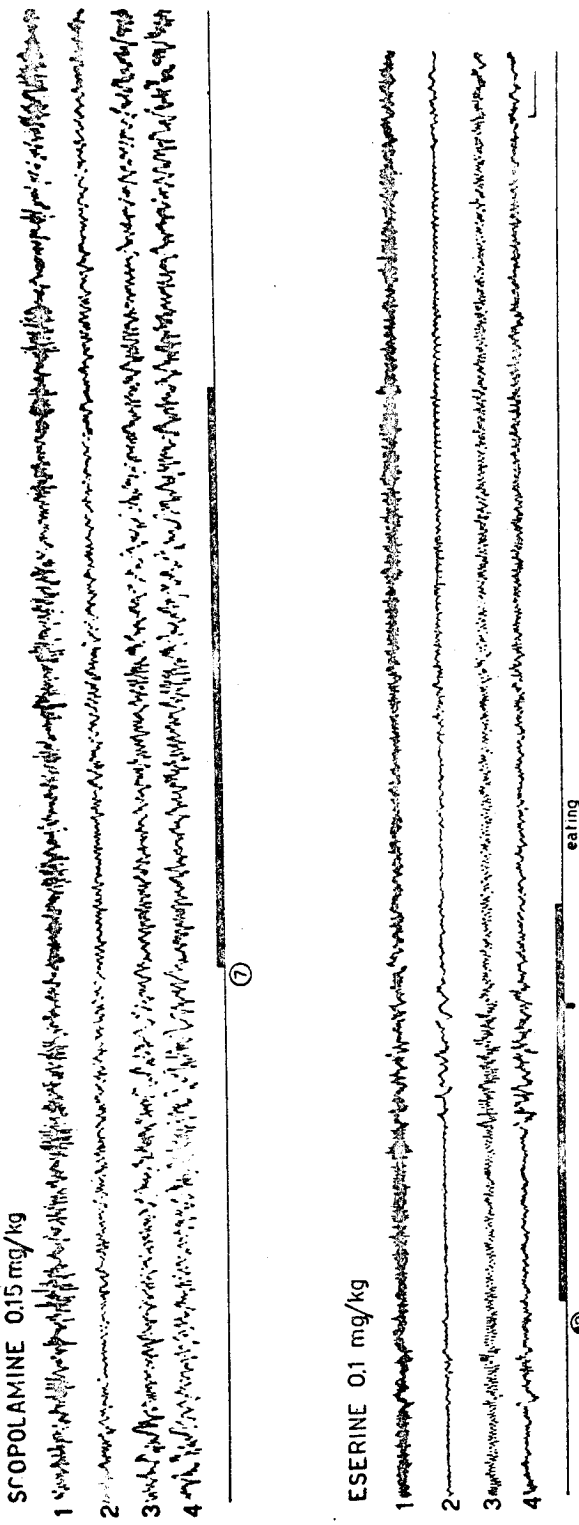

Fig. 4

Leads as in Fig. 3. Calibration: 100 μV, 2 sec. Antagonism between eserine and scopolamine effects in the ICR. Upper tracing: scopolamine in a dose of 0.15 mg/kg abolished the performance of the ICR and induced a synchronization of the tracing. No EEG activation is present upon the presentation of the CS. Lower tracing: eserine reactivates the ICR and the EEG activation patterns.

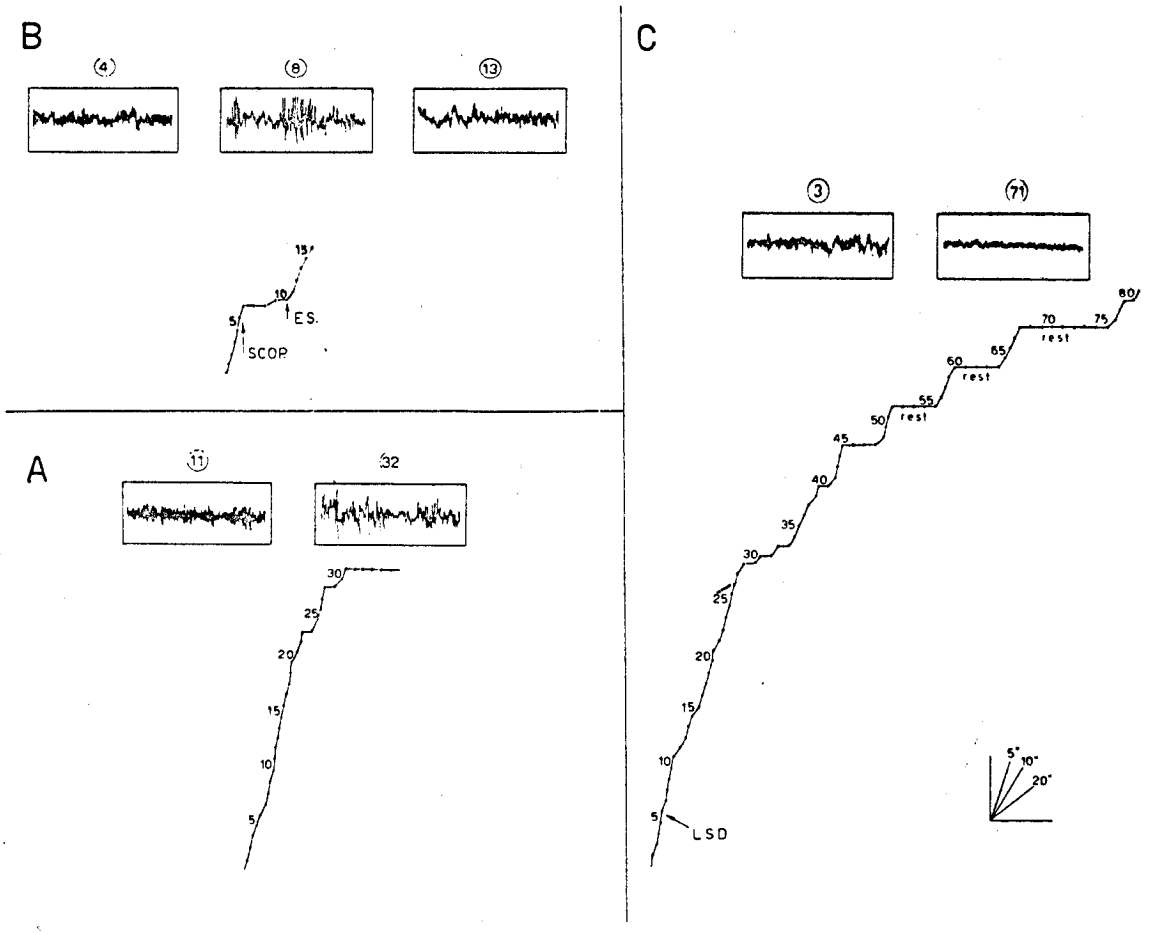

Fig. 5

The figures indicate graphically the performance of the ICR under various experimental conditions. Each trial is represented by a section of the curve between two points. The latency of the response is shown by the angle of inclination of the section. *A*: typical record obtained from an untreated animal. *B*: record obtained from an animal treated first with scopolamine and then with eserine. *C*: record obtained from an animal treated with LSD. The sample tracings (anterior sensorimotor cortex) shown were recorded during the trial indicated by the number.

severance of the response, *i.e.*, the rabbit performed the test for more than the average 20–30 times. With 3–5 mg/kg a more complex pattern appeared. The animals were very excited and performed running and searching movements around the cage. Upon the sound of the buzzer the rabbit approached the ring, pulled it, but did not take food from the cup. After several trials it ceased to respond to the CS. When food was placed in the cage independently of the conditioning procedure, the animal did not take it.

The EEG tracing presented continuous desynchronization patterns, even when the rabbit did not respond to the CS. When it was eating, well pronounced "masticatory" waves appeared in all the cortical and subcortical leads.

Imipramine was tested in ten experiments performed on three rabbits. Doses of 1–2 mg/kg did not, in two animals out of three, influence the performance of the ICR, whereas in the remaining one a facilitation was observed. Doses

of 5–10 mg/kg blocked the performance of the response in all the animals. Motor depression and postural disturbances developed after 5 mg/kg and after 10 mg/kg clonic seizures were noted. After the doses of 5 mg/kg or more, the animals ate food presented without the conditioning procedure, but did this more slowly, with long intervals of rest.

With the dose 5 mg/kg or more, a synchronization of the EEG tracing ensued which was not influenced by the CS. "Masticatory" waves were absent during the eating.

Lysergic acid diethylamide (LSD) was investigated in eleven experiments performed on three rabbits. With doses of 0.05–0.1 mg/kg a perseverance of the response, similar to that observed with the lower doses of amphetamine was observed, *i.e.*, the ICR was performed much longer than in the control experiments. There was a characteristic pattern involved in this prolongation. After having performed the average 20–30 pullings, the rabbit presented the usual behavioural signs of satiation. It then lay on the floor of the cage not responding to several applications of the CS. Afterwards it began to respond for a short period and then lapsed into another period of unresponsiveness (Fig. 5).

The EEG tracing was continuously activated, even during the periods of unresponsiveness, when the rabbit was lying on the floor. Only then did some slow waves appear, particularly in subcortical leads. When the animal ate the food, "masticatory" waves were usually diminished or abolished.

DISCUSSION

Electrophysiological and behavioural correlates of the ICR in rabbits.

There are at least two interacting components contributing to the behavioural and EEG changes in the animal performing the ICR. One is the relative degree of the animal's hunger and the other is the modification of neural activity resulting from the conditioning process. These two components must be kept in mind in considering the interpretations of the present results.

The EEG patterns accompanying the alimentary conditioned behaviour do not differ substantially from those described in the literature. In fact, activation of the EEG is known to occur during the performance of the conditioned response in cats (Galambos *et al.* 1956; Yoshii *et al.* 1957), dogs (Yoshii 1957; Trofimov *et al.* 1960), monkeys (Hearst *et al.* 1960) and men (Gastaut *et al.* 1957).

It should be pointed out, however, that in the present experiments the activation is not limited only to the period of the performance of the ICR, but is already present when the animal is placed in the cage. This can be explained by the fact that the hungry rabbit in the training box is influenced by environmental stimuli related to the alimentary conditioning. Although these stimuli do not evoke the conditioned response, they induce in the animal a state of behavioural and EEG alerting.

This picture can, however, be modified during the application of the CS and the performance of the exercise. These modifications are mainly observed at the hippocampal level and consist of an increase of the frequency and of the amplitude of the "theta" waves. If a localized EEG modification can be considered to be a clue to the underlying cerebral mechanisms, these changes in the hippocampal tracings might illustrate the situation in which a component of the limbic system plays a critical part in the performance of the ICR. This hippocampal activation was typically obtained, and it paralleled the performance of the instrumental response. On the contrary Grastián *et al.* (1959) described hippocampal activation in cats as related only to the early stages of the conditioning. The modifications of the tracing lasted only for the period from the onset of the sound until exercise was performed. Unlike other authors (Rougeul 1958), we did not find that the activation produced by the CS was further modified during the performance of the response.

In some instances, however, modifications were also obtained in the cortical tracing, particularly when the EEG of the animal waiting for the CS was characterized by the presence of 60–70 c/sec high voltage waves in the anterior cortical leads.

The EEG patterns share with the con-

ditioned response the phenomena of internal inhibition and also disinhibition by an extra-stimulus. In the present experiments, in fact, the cessation of the performance of the ICR was accompanied by synchronization of the tracing, which appeared in the rabbit after 20–30 positive responses. In this instance the two components mentioned above — hunger and the conditioning situation — are important. Typically, when the rabbit was transferred, after the day's test, into the animal house, it immediately consumed its daily ration. This suggests that the decline of the performance of the ICR and the synchronization of the EEG are, at least in part, the result of an inhibition resulting from the conditioning procedure. This inhibition is abolished by another environmental situation.

Regarding the "masticatory" waves, which seem to have been obtained only with the rabbit, further observations may be added to those previously described by Ectors (1936) and Longo (1960). Both these authors found that the "masticatory" waves disappeared during desynchronization of the tracing caused by external stimuli. In the present investigations it was noticed that the "masticatory" waves disappeared also when the tracing became synchronized, even though the animal continued to chew the food. Inhibition of the "masticatory" waves may thus be observed during two different states of cortical EEG activity: desynchronization and synchronization. The mechanism underlying inhibition of the "masticatory" waves is at present not understood. The disappearance of the rhythmic potentials might be due either to blocking at a subcortical relay or to inhibition at the cortical level.

Influence of drugs on the ICR and on the EEG activity

The sensitivity of the ICR to cholinergic drugs is the most clear-cut result of the pharmacological experiments. It was found that scopolamine was the most active drug which inhibited the ICR. This finding is contrary to that observed by Hearst (1959), who worked with thirsty rats trained to press a lever to obtain water upon presentation of one of two acoustic signals; he found that scopolamine disturbed the discrimination between two stimuli, but not the response to the positive stimulus presented alone.

In our experiments eserine counteracted the blocking effect of scopolamine on the ICR, if the doses of the two substances were adequately adjusted. The EEG modifications ran parallel to the occurrence of the conditioned motor response. In fact, synchronization of the tracing was observed after scopolamine, which changed to activation when eserine restored the performance of the ICR.

This observation modifies the wide-spread view that there is no parallelism between the electroencephalographic and the behavioural effects of cholinergic drugs in conscious animals, which has been pointed out by many authors (Wikler 1952; Rinaldi and Himwich 1955; Bradley 1958). This conclusion is correct only when it is based upon observation of general behaviour. When a sufficiently fine technique is applied, behavioural effects may be revealed. In the present experiments it was shown that scopolamine and eserine in doses almost as low as those influencing the EEG influenced behaviour. On the basis of these results, as well as those of other investigators, who have found a relationship between brain cholinesterase activity and adaptive behaviour in rats (Rosenzweig *et al.* 1960), it seems reasonable to suggest that the cholinergic system plays a role in the development of the plastic changes associated with learning, as well as in the maintenance of the conditioning response.

In the experiments with chlorpromazine a relative insensitivity of the ICR to this drug was found. Only the doses which produced motor depression and postural disturbances blocked the performance of the test. This observation is consistent with the results of Anokhin (1957, 1960), who also found a differential action of this drug on defensive and alimentary conditioned reflexes in rabbits. While the former are inhibited, the latter are not influenced or may even be facilitated. Also Cardo (1961) found that chlorpromazine reduced both the unconditioned and conditioned components of the avoidance response and delayed, but did not prevent, the acquisition of an instrumental reward response.

A similar phenomenon was observed after imipramine. This drug also blocks the ICR only with doses producing motor disturbances.

Amphetamine exerts two effects on the ICR. With low doses a perseverance of the response was observed. With higher doses the rabbits performed the exercise, but failed to take the food from the cup. This complex action of amphetamine could be explained in terms of a differential influence of this compound on the various components involved in the performance of the ICR. It is known that amphetamine facilitates conditioned behaviour (Gatti 1961), in so far as the conditioning requires a preliminary phase of exploratory activity, or it is dependent on the vigilance level of the animal. Cardo (1961) emphasized in particular the importance of the vigilance level in the performance of the conditioned exercise. On the other hand, amphetamine has a depressive action on the food intake, which has been explained as being due to either an excitation of the satiety center (Brobeck *et al.* 1956) or an inhibition of the hunger center in the hypothalamus (Stowe and Miller 1957). This negative effect of amphetamine on the food intake of conditioned animals was also described by Miller (1956) in rats trained to press a lever in order to obtain a food pellet. After amphetamine, although the number of pressings was increased, the amount of food consumed was diminished.

LSD also prolongs the ability of the animal to perform the ICR. This prolongation may be dependent upon sympathomimetic excitatory effects. However, unlike the results obtained with amphetamine, the high doses did not hinder food intake.

The effects of the various drugs on "masticatory" waves deserve some comments. The appearance of these waves seems to require a background of desynchronization. In fact, all drugs which produced synchronization of the tracing, also inhibited the appearance of the "masticatory" waves. On the other hand, the so-called desynchronizing drugs produced a reinforcement of the waves. This phenomenon was particularly evident with amphetamine. LSD, although it produced an EEG picture of activation, consistently inhibited the "masticatory" waves. This would indicate that the EEG activation provoked by LSD included some inhibitory components, which were not present with amphetamine. These results are consistent with findings of Longo (1962), who previously observed a differential effect of amphetamine and LSD on the EEG.

SUMMARY

In rabbits an instrumental reward conditioned response (ICR) was established. The animals were trained to pull a ring with the mouth when a buzzer sounded in order to obtain a piece of food (cabbage). The electrical activity of the cerebral cortex, the hippocampus and the thalamus was recorded by means of chronically implanted electrodes.

The EEG tracing of the rabbit, when it was first put into the cage, was activated and consisted of low voltage 25–30 c/sec waves in the cortex and 4–6 c/sec synchronous waves in the hippocampal leads. In the anterior cortex high voltage 60 c/sec waves sometimes appeared. When the conditioned stimulus was presented, the most striking changes were seen in the hippocampal lead, in which the synchronous waves increased in amplitude and frequency (up to 9 c/sec). In the period of satiation high amplitude slow waves at 2–3 c/sec, intermingled with spindles in the anterior cortex, appeared. The tracing was not further influenced by the CS.

During the eating period "masticatory" waves appeared, particularly in the anterior cortex. The tracing was less activated, and sometimes synchronized.

The ICR was found to be very sensitive to cholinergic drugs. Small doses of scopolamine (0.1 mg/kg) abolished it, but they did not interfere with the food intake. This action was accompanied by synchronization of the tracing. Eserine restored the performance of the test as well as the EEG activation patterns.

Chlorpromazine and imipramine exerted a blocking effect only in doses which produced motor disturbances. Particularly with chlorpromazine, the unconditioned food intake was not disturbed.

Amphetamine had two effects. In lower doses it facilitated the ICR. With higher doses

the pulling of the ring occurred, but was not folowed by taking the food from the feeding cup.

Lysergic acid diethylamide (LSD) had an effect similar to that of amphetamine in prolonging the performance of the ICR.

The appearance of "masticatory" waves was inhibited by scopolamine, chlorpromazine and imipramine, *i.e.*, by "synchronizing" drugs, as well as by LSD. Amphetamine, on the other hand facilitated these waves.

The present work demonstrates that the simultaneous study of conditioned behaviour and the EEG may be useful to explain some finer details of the central action of drugs.

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