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THE ACTION OF LOCAL ANAESTHETICS ON EXPERIMENTAL EPILEPSY IN CATS AND MONKEYS

BY

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Very little attention has been paid to the action of local anaesthetics on the functions of the central nervous system. In the current literature there is no mention of their striking effect, which will be dealt with in this paper, on experimental epileptic attacks and related central phenomena. A thorough search of the literature revealed two papers by Mercier (1950a and b) on the effect of different local anaesthetic drugs on audiogenic seizures in albino rats given subconvulsive doses of various convulsants. As far as we know no attention has been paid to these investigations, which seem to be the first to indicate that local anaesthetics, such as procaine, have an anticonvulsant effect.

We have studied the effects of different local anaesthetics on the electrically evoked epileptiform cortical after-discharge and related corticospinal phenomena, and compared them with the effects of these drugs on spinal functions and ascending transmission mechanisms. Preliminary reports on the central effects of lidocaine have already appeared (Bernhard and Bohm, 1954c and d). We have also compared the antiepileptic effect of these substances and barbiturates and of combinations of barbiturates and local anaesthetics. These investigations form the basis for the therapeutic use of a local anaesthetic, lidocaine (lignocaine A.N., "xylocaine"), for the rapid abolition of severe grand mal attacks and of post-operative epileptic seizures (Bernhard, Bohm, and Höjeberg, 1955).

METHODS

Cats and monkeys were used. Recordings of the epileptiform cortical after-discharge following repetitive cortical stimulation were made from the exposed brain. It is well known that the duration of the post-stimulatory epileptiform cortical after-discharge depends on such stimulation characteristics as total duration, frequency, and strength (see, for example, Noel, 1941; Walker and Johnson, 1948; Bernhard, Bohm, and Taverner, 1954), and on the narcotic level, as well as on the state of the cortex with reference to a preceding cortical stimulation (see, for example, Dusser de Barenne and McCulloch, 1937, 1939; Bernhard *et al.*, 1954). The type of cortical after-discharge and of the accompanying motoneurone activity, which in the non-curarized state results in epileptiform muscular convulsions, also varies with these different factors. Based on our recent studies of experimental epilepsy (Bernhard *et al.*, 1954), we used stimuli of about 1 msec. at 25/sec. for a total duration of 5 sec. The corticogram was recorded throughout the experiment, and cortical stimulation was not repeated until the corticographic changes from the preceding stimulation had disappeared. Usually there was a pause of 3–4 min. between each series of cortical stimulations. Pentobarbitone sodium, usually 15 mg./kg., was injected before the operation (opening of the skull, dissection of nerves, and sometimes laminectomy). Often 5 mg./kg. pentobarbitone was given after operation and before the stimulation, (+)-tubocurarine was added to prevent disturbing muscular contractions during the experimental epileptic attack. The narcotic level may have been different in the different experiments—an important point in the interpretation of the effects of the local anaesthetics. We have, therefore, made a closer study of the summation of the barbiturates and the local anaesthetics (see p. 293). Under conditions fixed with respect to the different factors mentioned, the duration of the epileptiform cortical after-discharge was surprisingly constant during a long period. In several experiments the action potentials were also led off from different nerves and ventral roots during and after repetitive cortical stimulation. In one series of experiments the mono- and polysynaptic reflex responses in the lumbar ventral roots to electrical stimulation of different nerves and dorsal roots were recorded. Finally, the response within the receiving area II of the cortex to afferent stimulation was led off with the same type of electrodes as those used for the corticograms (chlorided silver electrodes with a diameter of 0.5 mm.).

RESULTS

General Effect of a Local Anaesthetic on the Post-stimulatory Epileptiform Cortical After-discharge

Fig. 1 shows the corticograms (cat) from the frontal (tracing 1) and parietal (tracing 2) areas

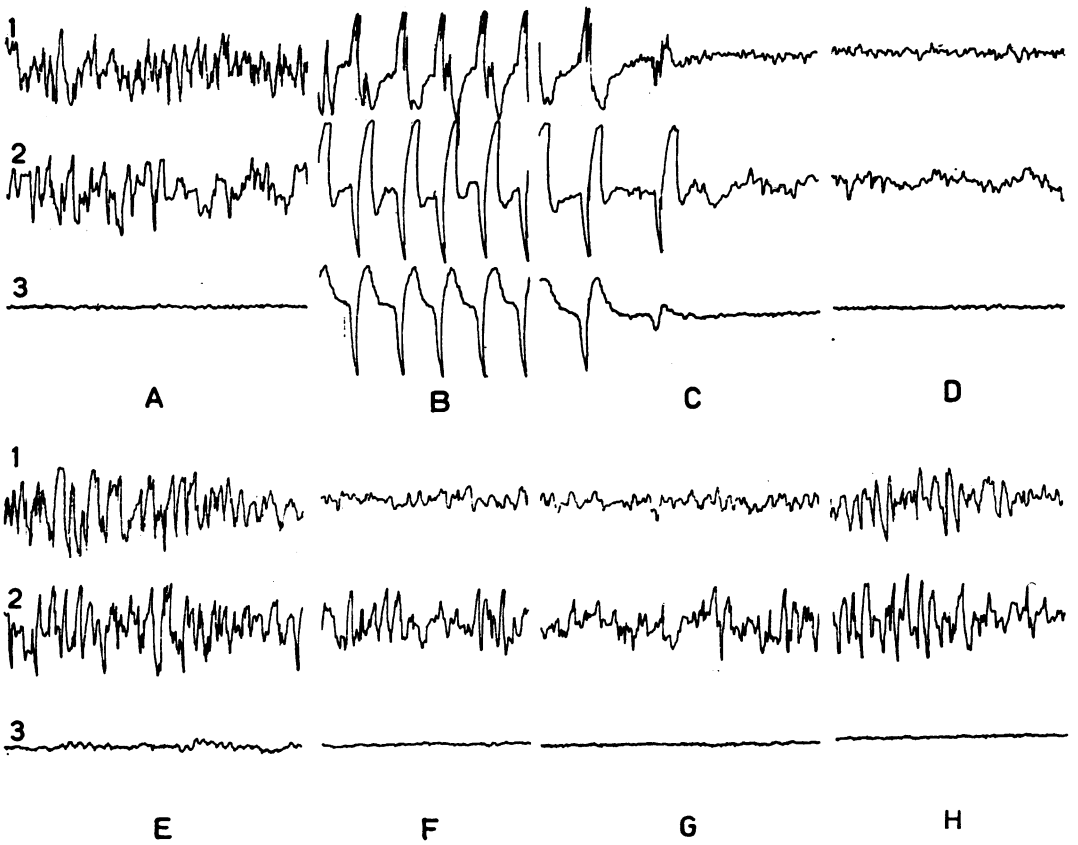

FIG. 1.—Cortical activity led off from the frontal (tracing 1) and parietal (tracing 2) areas in cat before (A–D) and 5 min. after (E–H) intravenous injection of 2 mg./kg. lidocaine. A and E before stimulation; B and F 5 sec., C and G 15 sec., D and H 25 sec. after cessation of repetitive cortical stimulation (25/sec., for 5 sec.) of the ipsilateral sensorimotor area.

ipsilateral to the stimulating electrodes placed within the precentral region. Tracing 3 is from the L7 ventral root contralateral to the cortical area stimulated. Repetitive cortical stimulation elicited a typical epileptiform after-discharge (Fig. 1 B–C). The hypersynchronous cortical potentials as well as the rhythmical outbursts of "clonic" type in the L7 ventral root continued for 12 sec. after the cessation of the repetitive stimulation, and their frequency decreased in a typical way before they finally disappeared (Fig. 1 C). This convulsive attack was followed by a diminution ("exhaustion") of the cortical potentials (Fig. 1 C and D). An intravenous injection of lidocaine (2 mg./kg. in 1% w/v solution) was then given, and 5 min. later the cortex was again stimulated. Records F–H in Fig. 1 show that the injection of the lidocaine was followed by a total abolition of the poststimulatory epileptiform attack and that the cortical "exhaustion" was less pronounced than before the injection (*cf.* Fig. 1 D and H), whereas it had no significant effect on the prestimulatory corticogram (*cf.* Fig. 1 A and E).

The recovery of the poststimulatory after-discharge was investigated by testing the effect of cortical stimulation at various intervals after the injection. The injection of 2 mg./kg. lidocaine usually caused a total abolition of the cortical after-discharge for 10–15 min. followed by recovery to the pre-injection value in about 60 min. (filled circles in Fig. 2). A smaller dose (1 mg./kg.), however, generally did not produce a complete block but reduced the duration of the poststimulatory epileptiform attack to 30–50% of the pre-injection value (open circles in Fig. 2). Fig. 2 also shows the surprising constancy, in the absence of a drug, of the duration of the cortical after-discharge for 60 min. (crosses)—a necessary condition for our test experiments.

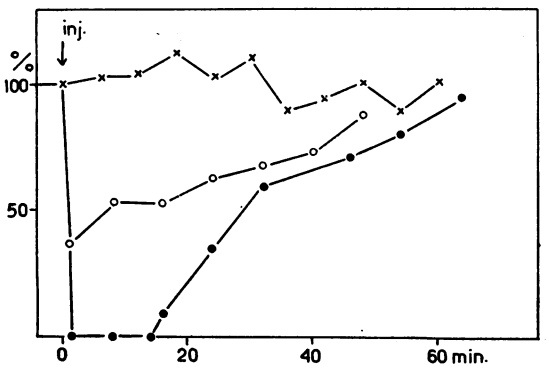

FIG. 2.—Duration of cortical after-discharge as a percentage of pre-injection values (vertical axis) plotted against time (horizontal axis) after intravenous injection of 1 mg./kg. (open circles) and 2 mg./kg. (filled circles) of lidocaine. The crosses represent individual duration values of cortical after-discharge obtained during 60 min. before injections. The filled circles are from the experiment in Fig. 1.

It should be mentioned that slow intravenous injections of lidocaine, in the doses used in these experiments, are known not to influence the blood pressure (Goldberg, 1949); we also confirmed this.

Comparison of Different Local Anaesthetics on the Poststimulatory Cortical After-discharge

Different intravenous doses (0.5–4 mg./kg.) of procaine, butethamine (*iso*butylaminoethyl *p*-aminobenzoate, " monocaine "), lidocaine (diethylaminoacetat-2:6-xylidide), diethoxine (diethylaminoethyl 4-ethoxylbenzoate hydrochloride), and tetracaine (2-dimethylaminoethanol 4-*n*-butylaminobenzoate hydrochloride, amethocaine) were tested in cats and monkeys. All of them, depending upon the dose, blocked or diminished the epileptiform after-discharge. The curves in Fig. 3 illustrate the protective action against experimental epileptic fits of 2 mg./kg. of the drugs mentioned. Fig. 3 gives the results from a series of experiments performed on the same preparation under similar conditions. As seen, lidocaine was more effective than procaine and butethamine. The two latter substances had about the same effect on the cortical after-discharge. Diethoxine, however, was of about the same potency as lidocaine. Tetracaine, finally, always gave a more prolonged effect than lidocaine. To evaluate the effect of these substances on the cortical after-discharge, several series of experiments were performed, the drugs being given in such amounts that they only produced a partial block (see curves for procaine and butethamine in Fig. 1). For example, in one series of experiments the doses of the different local anaesthetics which gave a reduction of the duration of the cortical after-discharge to 50% were found to be 3 mg./kg. for procaine, 2 mg./kg. for butethamine, 1 mg./kg. for lidocaine and diethoxine, and 0.2 mg./kg. for tetracaine. The experiments referred to were all performed on cats. Our experiments on the antiepileptic effects of the different local anaesthetics in monkeys gave similar results.

One of the main reasons for these introductory investigations was to find which substances of this type would be most convenient as anticonvulsants in certain clinical conditions (*cf.* Bernhard, Bohm, and Höjeberg, 1955). As shown above, tetracaine was the most efficient, but it would not be convenient for clinical intravenous use because of its relatively high toxicity. Of the others lidocaine and diethoxine were the most potent. Since lidocaine seems to be less toxic than diethoxine and since, in addition, there is considerable evidence that the intravenous injection of lidocaine in man carries little risk of complications (Clive-Lowe, Gray, Spencer and North, 1954), lidocaine was the chief drug used in our further investigations on the central effects of local anaesthetics.

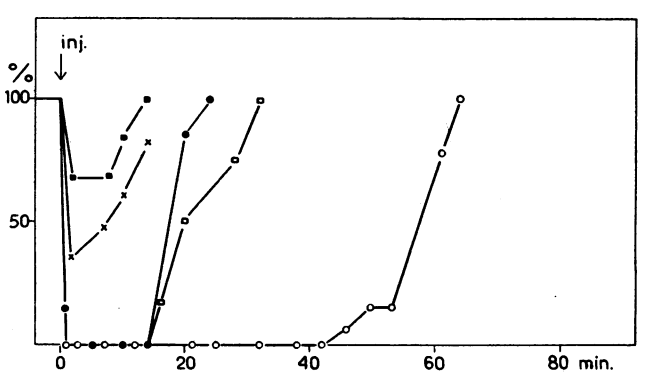

FIG. 3.—Duration of cortical after-discharge as a percentage of pre-injection values (vertical axis) plotted against time (horizontal axis) after intravenous injection of 2 mg./kg. of different local anaesthetics. Filled rectangles, procaine; crosses, butethamine; filled circles, lidocaine; open rectangles, diethoxine; open circles, tetracaine.

The Antiepileptic Effect of Lidocaine Compared with its Effect on Other Central Functions

So far we have only discussed the duration of the after-discharge, since this characteristic of the epileptiform attack seemed to be valuable for the study of anticonvulsants on this specific central phenomenon (see Bernhard *et al.*, 1954). The epileptiform motoneurone activity evoked by electrical cortical stimulation often shows a " tonic-clonic " phase followed by a " clonic " phase (see Rosenblueth, Bond, and Cannon, 1942 ; Jasper, 1954 ; Bernhard *et al.*, 1954) the electrical signs of which can be recorded from the ventral root. In Fig. 4, obtained from an experiment on a monkey, the heavy line at the top marks the total duration of the cortical after-discharge (12 sec.) following cessation of repetitive cortical stimulation (zero at the horizontal axis), and the thin line immediately beneath it marks the duration of the " tonic " component of the poststimulatory L7 ventral root activity. During the first period of the poststimulatory phase the segmental monosynaptic reflex was greatly facilitated. In earlier investigations we have shown how this facilitatory action on the motoneurones is built up during repetitive cortical stimulation, and how the facilitation continues after cortical stimulation has stopped (Bernhard and Bohm, 1954b). Fig. 5 shows the monosynaptic reflex in L7 ventral root elicited by stimulation of the biceps nerve before (A) and after (B) repetitive cortical stimulation. The monosynaptic reflex, tested at different intervals after cessation of cortical stimulation, was facilitated (Fig. 4, dashed curve) for 3–4 sec. after cessation of stimulation, that is for about the same time as the " tonic after-discharge " (thin horizontal line). The facilitation was followed by a depression of the monosynaptic

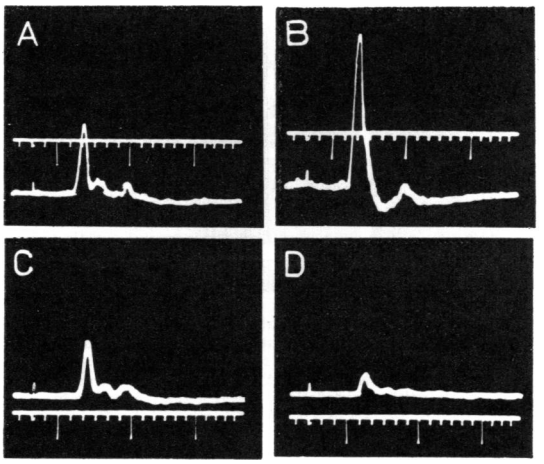

FIG. 5.—Monosynaptic reflex response in L7 ventral root following stimulation of the ipsilateral biceps nerve in monkey. A, before cortical stimulation; B, 2 sec. after conditioning repetitive cortical stimulation (25/sec., for 5 sec.) of the contralateral precentral region. C and D, the same after 3 mg./kg. lidocaine i.v.

reflex for about 20 sec. (*cf.* Bernhard *et al.*, 1954). After the injection of 2 mg./kg. lidocaine the cortically evoked poststimulatory facilitation of the monosynaptic reflex disappeared entirely (Fig. 5 C and D). Fig. 4 shows the amplitude changes of the monosynaptic reflex during the poststimulatory period 3 (a), 8 (b), and 14 (c) min. after the injection of lidocaine. The amplitude of the monosynaptic reflex was decreased during the poststimulatory period after the lidocaine, which in this experiment blocked the poststimulatory after-discharge for 14 min.

This experiment shows that the cortically evoked poststimulatory facilitation of the monosynaptic

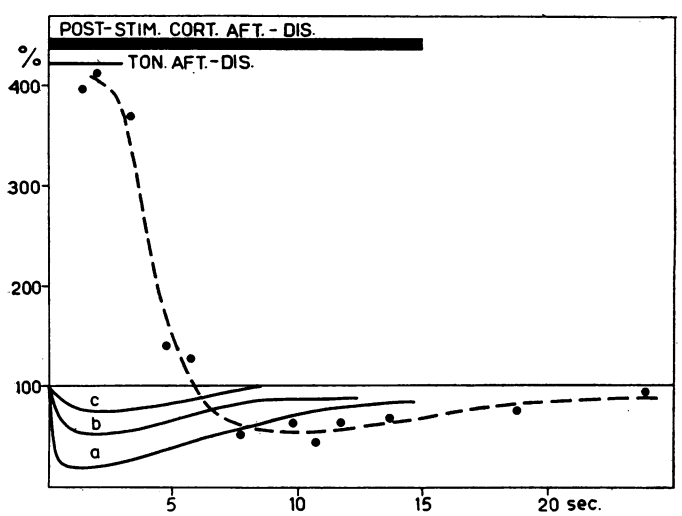

FIG. 4.—Amplitude of the monosynaptic reflex response in the L7 ventral root to stimulation of the ipsilateral biceps nerve during the period following the cessation (zero on horizontal axis) of conditioning repetitive cortical stimulation (25/sec., for 5 sec.) of the contralateral precentral area. The amplitude values are given as a percentage of the unconditioned values obtained before cortical stimulation (100% on vertical axis). Dashed curve shows the poststimulatory facilitation and subsequent depression of the monosynaptic reflex before the injection of 3 mg./kg. lidocaine. Curves a, b, and c (unbroken) show the poststimulatory depression of the monosynaptic reflex after the injection of 3 mg./kg. lidocaine. Heavy line marks the duration of the poststimulatory cortical after-discharge and the thin line the duration of the tonic phase of the poststimulatory ventral root activity before the injection of lidocaine. Monkey.

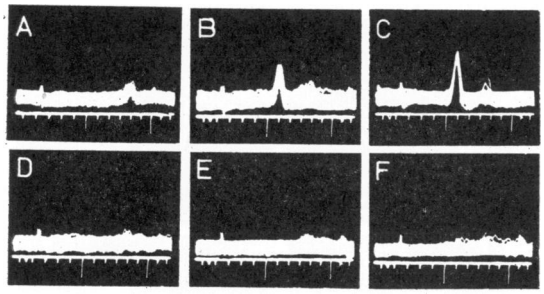

FIG. 6.—Superimposed action potentials in the left radial nerve following each stimulus in a train of shocks (25/sec.) delivered to the fore limb subdivision of the right precentral cortical area 1 (A and D), 3 (B and E), and 5 (C and F) sec. after the beginning of the repetitive stimulation, before (A–C) and 3 min. after intravenous injection of 4 mg./kg. lidocaine (D–F). Time in msec. Monkey.

reflex disappears in parallel with the abolition of the epileptiform attack.

The response in different nerves or ventral roots to each cortical stimulus in a train of repetitive shocks consists of a series of action potentials with different latencies. Fig. 6 A–C shows a series of superimposed records of the action potentials in the radial nerve of a monkey following each cortical stimulus in a train of shocks (25/sec.) at different intervals after the beginning of the repetitive stimulation. In our earlier investigations evidence was presented that in *monkeys* the earliest response which is built up during the repetitive cortical stimulation is monosynaptically transmitted from the corticospinal neurones to the motoneurones (Bernhard, Bohm, and Petersén, 1953; Bernhard and Bohm, 1954a and b). The building up of this monosynaptic response during the course of the repetitive cortical stimulation is shown in Fig. 7 A (filled circles). According to the earlier investigations mentioned, the increase of the monosynaptic response to cortical stimulation reflects the building up of cortically evoked facilitatory effect, the poststimulatory phase of which is represented by the dashed curve in Fig. 4.

It was therefore of interest to investigate the effect of the local anaesthetics on the building up of the monosynaptic motoneurone response to cortical stimulation. Records 6 D–F were taken 3 min. after injecting lidocaine (4 mg./kg.) at the same intervals during the repetitive cortical stimulation as records 6 A–C which were taken before injecting lidocaine. No monosynaptic response was built up during the stimulation period used (open circles in Fig. 7 A). Fig. 7 B shows that the cortical after-discharge evoked by the repetitive stimulation was also totally abolished 3 min. after the injection of lidocaine. Six min. after the injection (crosses in Fig. 7 A) the monosynaptic response to each cortical shock slowly built up to the original value and the cortical after-discharge had recovered to 40% of the pre-injection value (see Fig. 7 B). Finally, 11 min. after the injection, the building up of the monosynaptic response (rectangles in Fig. 7 A) was normal, and the cortical after-discharge had recovered (see Fig. 7 B).

In contrast to the very striking blocking effect on the poststimulatory epileptiform attack, as well as on the corticospinal facilitatory action during the repetitive cortical stimulation, the same doses of local anaesthetics had comparatively little influence on certain other central functions. In cats the effects of lidocaine on the amplitude of the monosynaptic and polysynaptic reflexes were tested as well as its effects on the cortical area II responses to electrical stimulation of low threshold fibres in cutaneous nerves. The effect on the cortical after-discharge to cortical stimulation was tested in the same experiments. Typical results of such an experiment are shown in Fig. 8. The reflex responses were reduced to 70–90% of the pre-injection values, during the period when the cortical after-discharge was totally abolished by lidocaine and there was no effect at all on the amplitude of the cortical response to the ascending volley elicited by stimulation of low threshold cutaneous afferents. In other experiments of this type, and in experiments on non-anaesthetized spinal preparations, the amplitudes of the reflex responses were only slightly reduced or unaltered by the injection of a similar dose of lidocaine.

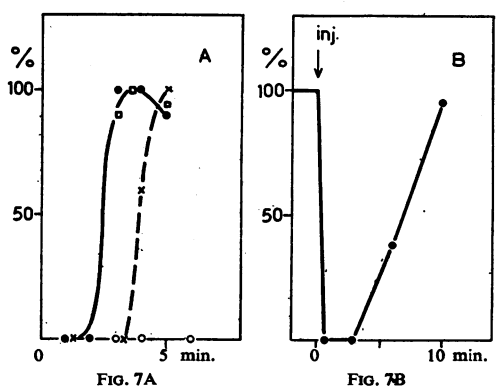

FIG. 7A

FIG. 7B

FIG. 7A.—Amplitude of the monosynaptic response in the radial nerve to contralateral cortical stimulation at different intervals after the beginning of the repetitive cortical stimulation as a percentage of the highest value obtained. Filled circles (unbroken curve) before lidocaine; open circles 3 min., crosses (dashed curve) 6 min., after 2 mg./kg. lidocaine i.v.

FIG. 7B.—Duration of the poststimulatory cortical after-discharge as a percentage of pre-injection values plotted against time after the injection of 2 mg./kg. lidocaine. Monkey.

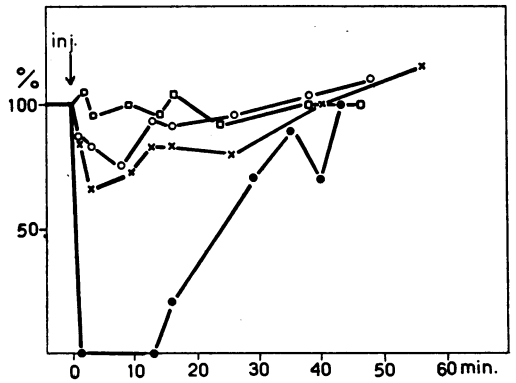

FIG. 8.—Effects of 2 mg./kg. lidocaine i.v. on the duration of the cortical after-discharge (filled circles), monosynaptic reflex (crosses), polysynaptic reflex (open circles) and sensory area II response to stimulation of low threshold afferent fibres (rectangles). The values for the duration of the cortical after-discharge as well as for the amplitude of the potential responses are plotted as a percentage of the pre-injection values against time after the injection.

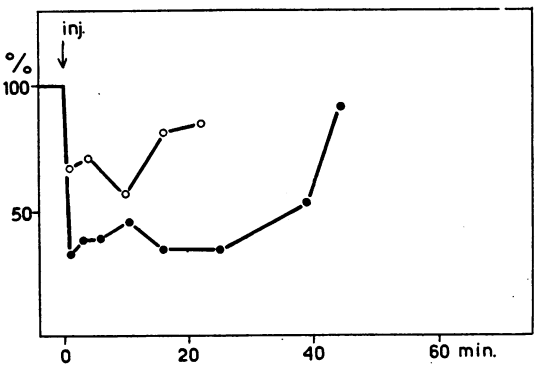

FIG. 9.—Duration of cortical after-discharge as a percentage of the pre-injection values plotted against time after the injection of 1 mg./kg. lidocaine (open circles) and 3 mg./kg. phenobarbitone (filled circles).

Comparison of the Action of Lidocaine and Barbiturates, and Summation of Their Effects, on the Cortical After-discharge

The effect of phenobarbitone (3 mg./kg.) on the cortical after-discharge was compared with that of lidocaine (1 mg./kg.) in a cat under light pentobarbitone anaesthesia (Fig. 9). The experiment shows that—in such a preparation at least—lidocaine is more effective in blocking the cortical after-discharge than is phenobarbitone.

Since, as mentioned, all our experiments were on cats and monkeys under pentobarbitone, and since the barbiturates themselves influence the cortical after-discharge, it was of importance to obtain information about the summation of the effects of pentobarbitone and a local anaesthetic on the cortical after-discharge. This is shown in Fig. 10 A and B for pentobarbitone and lidocaine in a monkey. A small dose of pentobarbitone (15 mg./kg.) was given before opening the skull. The average duration of the cortical after-discharge was then estimated. The average pre-injection value of the duration of the cortical after-discharge was 12 sec. Lidocaine (1 mg./kg.; arrow 1 in Fig. 10 A), in this lightly anaesthetized preparation, did not have any significant effect on the duration of the cortical after-discharge. Thirteen min. after the lidocaine, pentobarbitone (1 mg./kg.) was injected; this dose did not have any effect on the cortical after-discharge either (arrow 2 in Fig. 10 A). Eight min. later a further lidocaine injection (1 mg./kg.; arrow 3 in Fig. 10 A) was followed by a dramatic effect on the cortical after-discharge, its duration being reduced to about 20% of the pre-injection value. Experiments of this type show

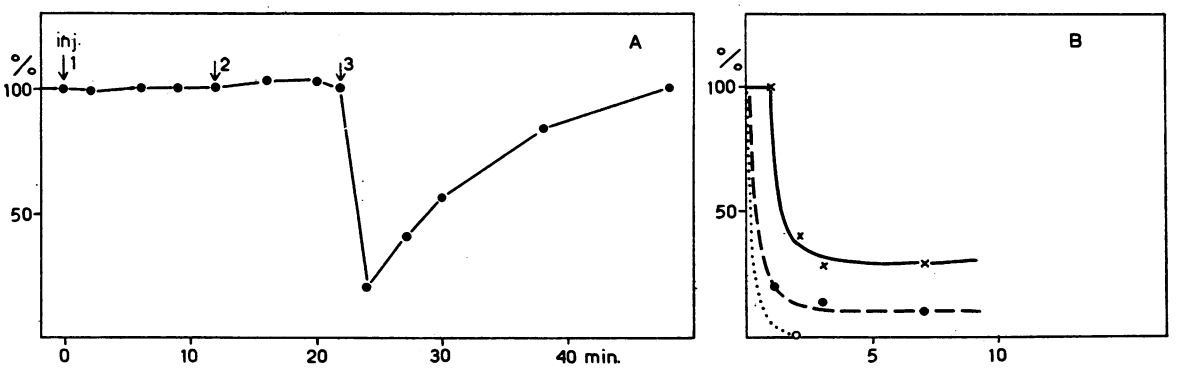

FIG. 10.—Summation effect of lidocaine and pentobarbitone on the poststimulatory cortical after-discharge. (A) Duration of cortical after-discharge as a percentage of pre-injection values plotted against time. Arrows 1 and 3 mark injections of 1 mg./kg. lidocaine, and arrow 2 marks the injection of 1 mg./kg. pentobarbitone. (B) Crosses show the duration of cortical after-discharge as a percentage of pre-injection values plotted against the amount of pentobarbitone injected. Circles show the duration of the cortical after-discharge as a percentage of the pre-injection values after the injection of 1 mg./kg. (filled circles) and 2 mg./kg. (open circles) lidocaine plotted against dose of pre-injected pentobarbitone (mg./kg.).

that pentobarbitone in small doses increases the sensitivity of the cortical after-discharge to the local anaesthetic.

Fig. 10 B, obtained from the same experiment, shows how, up to a certain point, the injection of increasing doses of pentobarbitone increased the sensitivity to lidocaine (1 mg./kg.). The effect on the duration of the cortical after-discharge of different doses of pentobarbitone alone is included: at 1 mg./kg. there was no effect, but 2 mg./kg. reduced the duration of the after-discharge to 40%. It is of interest that a further increase (up to 7 mg./kg.) only caused a reduction of the duration of the after-discharge to about 30% ; it was never abolished. Lidocaine (1 mg./kg.) had no influence on the cortical after-discharge before, but reduced it to 20% after, the pentobarbitone ; the pentobarbitone alone had no effect. Larger doses of pentobarbitone increased the effect of lidocaine (1 mg./kg.) only slightly. If, instead, 2 mg./kg. of lidocaine was injected after 1 mg./kg. of pentobarbitone, the after-discharge was totally abolished (dotted curve in Fig. 10 B). Some important general implications of these results will be taken up in the discussion. Here it should only be stressed that the amount of pre-injected pentobarbitone, up to a certain dose, modifies the sensitivity of the cortical after-discharge to local anaesthetics. Because of this fact we tried to keep the different preparations on the same narcotic level when testing the effect of the different local anaesthetics on the cortical after-discharge.

Discussion

It is perhaps not surprising that there has been relatively little mention in the current literature of the effects of local anaesthetics on the central nervous system, because several central functions —for example, the spinal reflexes and the transmission in the ascending system connected to low threshold afferent fibres—were found to be very little affected by intravenous injections of local anaesthetics in moderate doses (see Fig. 8). This is in striking contrast to the pronounced blocking effect of the same doses of the drugs on the poststimulatory epileptiform cortical after-discharge. Further investigations are being performed in order to find the mode and site of action of these drugs in the complex mechanisms—known to be both cortical and subcortical—involved in the epileptiform attack (see, for example, Jasper, 1954). The facts that the pre-stimulatory corticograms, as well as the cortical response within the cortical receiving area II, are not significantly altered, indicate that the excitability of at least part of the cortical neurones is not affected by doses which produce a total abolition of the poststimulatory after-discharge. It is interesting to note that the facilitatory effect on the motoneurones built up by cortical stimulations (Figs. 6 and 7), which persists after the cessation of the repetitive cortical stimulation (Figs. 4 and 5), is abolished by lidocaine in parallel with the abolition of the cortical after-discharge. There are reasons to assume that this effect is owing to an action on the transmission systems mediated over the bulbar reticular formation, the functions of which have been thoroughly investigated by Magoun and his colleagues (Magoun, 1950), but we have not tested this assumption experimentally.

It should also be mentioned that the blocking effect of the local anaesthetics on the cortical after-discharge offers a means of studying the different steps in the elicitation of experimental epilepsy. For instance, during the period when the cortical after-discharge is abolished after the injection of lidocaine, some of the post-stimulatory effects on different spinal functions may still be present in the absence of the cortical after-discharge (Fig. 4, curves a–c). Thus different kinds of corticospinal activity may continue as the result of the cortical stimulation by itself and not as a result of the epileptiform attack—in contrast to certain forms of corticospinal activity which are due to the poststimulatory epileptic fit.

Among the different local anaesthetics tested tetracaine was found to have a more pronounced protective effect against the poststimulatory cortical after-discharge than lidocaine and diethoxine, these two substances being more effective than butethamine and procaine. The order of effectiveness of these substrates as local anaesthetics (see, for example, Wiedling, 1953 ; Gray and Geddes, 1954) seems to be the same as that of their effectiveness as anticonvulsants. In this connexion, however, it should be mentioned that other substances which are active as local anaesthetics had an opposite effect on the duration of the cortical after-discharge: it is thus not possible to conclude that there is a direct relationship between local anaesthetic activity as such, and anticonvulsant activity.

Our study of the summation effect of a local anaesthetic and a barbiturate shows (1) that the administration of pentobarbitone alone reduces the duration of the cortical after-discharge, but, even in relatively big doses, does not abolish it ; (2) that small doses of pentobarbitone increase the sensitivity of the cortical after-discharge to lidocaine, but that this effect reaches a maximum after quite small doses of pentobarbitone ; (3) that only a small increase of the lidocaine dose is followed

by a total abolition of the cortical after-discharge in preparations which have received a small dose of pentobarbitone.

The effect of the local anaesthetics against experimental epileptic attacks seems to us to be quite striking. Since, however, the experiments were performed on animals under light pentobarbitone anaesthesia they do not prove the effectiveness in the absence of barbiturates. However, we have already found that moderate doses of intravenously injected lidocaine stop status epilepticus in man not given any other anticonvulsant drugs (Bernhard, Bohm, and Höjeberg, 1955). The reasons for using lidocaine in most of these studies, which serve as a basis for the clinical application, have already been mentioned. It should only be added that the results of the experiments on the summation effects of lidocaine and pentobarbitone have been confirmed in investigations in man (Bernhard, Bohm, Höjeberg, and Melin, 1955). The conclusion is that a combination of a small dose of barbiturate with lidocaine is the most effective treatment for the temporary abolition of severe epileptic fits. In this way, also, excitatory effects of lidocaine, which have very rarely been observed after injection in man (Clive-Lowe, Gray, Spencer, and North, 1954), are avoided.

Summary

1. The effects of local anaesthetics (procaine, butethamine, lidocaine, diethoxine, and tetracaine) on experimental epilepsy, as well as on other types of central activity, are described in cats and monkeys—under light pentobarbitone anaesthesia.

2. Intravenous injections of these local anaesthetics reduce or abolish the poststimulatory epileptiform cortical after-discharge elicited by cortical stimulation, without altering the prestimulatory EEG. The effect depends on the dose and on the degree of anaesthesia. Tetracaine is more effective than lidocaine and diethoxine, and lidocaine and diethoxine are more effective than procaine and butethamine. Taking into account the relation between the toxicity of these substances and their effectiveness against experimental epilepsy, lidocaine appears to be the most suitable anticonvulsant for clinical use.

3. Lidocaine, in doses which block the epileptiform cortical after-discharge, abolishes the cortically evoked facilitatory effect on the spinal motoneurones which is built up during the repetitive cortical stimulation. In connexion with these findings some aspects of experimental epilepsy are discussed.

4. Lidocaine, in doses which abolish the experimental epileptic fit, has no significant effect on the spinal reflexes; the monosynaptic and polysynaptic reflexes may be reduced only to 70–90% of the pre-injection values. Finally, the cortical response within the sensory area II to ascending volleys evoked by stimulation of low threshold cutaneous fibres is not influenced at all by lidocaine in doses which abolish the experimental epileptic attack.

5. The experiments on the summation effects of a barbiturate (pentobarbitone) and lidocaine show (1) that pentobarbitone alone, in suitable doses, reduces the duration of the epileptic fit; (2) that the injection of pentobarbitone in doses too small to affect the epileptic fit, increases the anti-epileptic effect of lidocaine; (3) that even 2 mg./kg. lidocaine abolishes the epileptic fit in preparations which have received a small dose of pentobarbitone (20–25 mg./kg.).

6. We conclude that a combination of a small dose of a barbiturate and a moderate dose of lidocaine should be used for the temporary abolition of epileptic fits in man.

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