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# A PROPOSED COMMON MECHANISM OF ACTION FOR GENERAL AND LOCAL ANAESTHETICS IN THE CENTRAL NERVOUS SYSTEM

BY

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Procaine and several general anaesthetics block production of action potentials in frog skeletal muscle fibres by a single mechanism of action, which suggests that there might be a common basic mechanism of action on neurones in the central nervous system. Procaine or cinchocaine given alone to intact white mice produced "excitement" and convulsions but when given 60 min after phenobarbitone they caused central nervous depression. Large, convulsant doses of procaine or cinchocaine abolished the righting reflex in mice previously treated with small, subanaesthetic doses of phenobarbitone. In contrast, leptazol only antagonized the depression produced by phenobarbitone. When applied directly to neuronally isolated slabs of cat cerebral cortex, procaine or pentobarbitone reduced the sizes of the surface negative and surface positive responses to direct electrical stimulation of the cortex. Leptazol had the opposite effect. When given systemically, procaine only increased the electrical threshold for the surface positive response recorded from the isolated slab; ether either increased or did not change this threshold, and leptazol either decreased or did not change it. These results are consistent with the suggestion that general and local anaesthetics have a fundamentally similar action on neurones in the central nervous system.

In 1956 Thesleff studied the effects of several non-volatile general anaesthetic drugs on the electrical activity of skeletal muscle fibres. He found that each of these agents blocked the production of action potentials by inhibiting the specific increase in sodium conductivity of the membrane which normally follows an adequate stimulus. An identical effect and mechanism of action has since been shown for chloroform (Yamaguchi, 1961) and ether (Yamaguchi, 1961; Inoue & Frank, unpublished). Thesleff (1956) also compared the ability of drugs to produce an hypnotic effect in intact frogs with their ability to affect the electrical activity of muscle cells. The doses required to produce these two distinct effects were similar and he suggested the possibility that these drugs produced hypnosis and general anaesthesia by an action on the electrical excitability of cells in the central nervous system identical to that observed in skeletal muscle fibres.

More recently Inoue & Frank (1962) found that procaine also blocks the production of action potentials in skeletal muscle fibres by suppressing the increase in sodium conductivity. Since this effect is produced both by general anaesthetics

and by procaine, they suggested the possibility that local and general anaesthetic drugs had a single basic mechanism of action on cells in the central nervous system.

If this suggestion is to be considered seriously, some explanation of the seemingly different effects of drugs of these two groups on the gross activity of the central nervous system must be proposed. One obvious explanation would be that both groups can produce " excitement " by a single mechanism, possibly by suppression of inhibitory neurones, which is different from the mechanism of action of stimulants such as leptazol. With the general anaesthetics this excitement is characteristic of Stage II anaesthesia (Guedel, 1951).

The present paper presents the results of experiments designed to test the suggestion that general and local anaesthetics have a fundamentally similar action on neurones in the central nervous system. In the first series of experiments the drugs were injected intraperitoneally into mice either alone or after phenobarbitone, to find out whether local anaesthetics would potentiate or antagonize the action of the general anaesthetic phenobarbitone. In the second series of experiments, isolated slabs of the cat cerebral cortex were used to compare the effects of procaine, ether and pentobarbitone on the evoked electrical responses of cerebral cortical neurones. In both series of experiments, leptazol, a convulsive agent having no local anaesthetic action, was used for comparison.

## METHODS

*Effects of drugs on the motor activity of intact mice.* Drugs were injected in a volume of 0.1 to 0.2 ml. intraperitoneally into female Swiss Albino mice (Lemberger Co.) weighing between 20 and 30 g. Gross effects on motor activity were observed and noted. Loss of the righting reflex without prior convulsive activity was used as a criterion of central nervous depression. Two other criteria employed were whether the animal eventually recovered and whether the withdrawal response to pinching the foot could be elicited, which indicated the persistence of spinal reflexes. Although not completely satisfactory, these criteria did establish the existence or absence of a condition which was otherwise indistinguishable from general anaesthesia. Unequivocal hyperkinesia without loss of the righting reflex was taken to indicate uncomplicated " excitement."

During tests of the response to each drug by itself, the animals were observed for 15 min following the administration of procaine hydrochloride or cinchocaine hydrochloride, and for 60 min following pentobarbitone sodium. For drug interaction studies, pentobarbitone was administered 60 min before the local anaesthetic to be certain that the maximum response to the general anaesthetic had been obtained. The animals were observed for an additional 15 min following the subsequent administration of the local anaesthetic. The dose/response curves were analysed and compared by the methods of Litchfield & Wilcoxon (1949).

*Effects of drugs on the cerebral cortex.* Neuronally isolated slabs of unanaesthetized cat cerebral cortex were prepared as described by Burns (1951) and by Burns & Grafstein (1952). Although neuronal connections between the slab and the rest of the brain were severed, the slab still received its usual blood supply from the pia mater and responded to direct stimulation. The cats were decerebrated by a midcollicular section during ether anaesthesia; at least 1 hr was allowed to elapse before testing to permit the ether to be excreted.

Rectangular electrical pulses from Tektronix pulse and waveform generators (Types 161 and 162) were delivered through bipolar platinum electrodes with ball tips which rested on the surface of the exposed cortex about 1.5 mm apart. The recording electrodes consisted of saline-agar filled glass tubing with a silk thread embedded in the agar and extending from one end. The moist silk thread lay on the cortex and a chlorided silver wire inserted

in the agar was connected to an amplifier and recorder. Monopolar recordings were obtained by placing one recording electrode on the cortical surface 1 to 5 mm from the stimulating electrodes and the other on a killed reference area at one end of the slab. The responses were amplified by a differential DC amplifier (Princeton Science Associates, Model TA-2) and displayed on a Tektronix oscilloscope (Model 502). Measurements were made from photographic records.

In all experiments, the exposed bone and cerebral cortex were covered with mineral oil. Rectal temperature was measured with a thermometer and when necessary a warming plate or a heating lamp was used to maintain a temperature between 35° and 37° C. Femoral arterial blood pressure was measured by a mercury manometer.

Two different procedures were used for applying and testing drugs. In one, a strip of filter paper 1×5 mm was moistened (but not saturated) with 0.9% saline and placed across the width of the slab. The recording electrode was placed either on top of this strip or on the cortex at the edge of the strip nearest to the stimulating electrodes. A stimulus intensity was chosen which would produce a surface negative response followed by a surface positive burst (Burns, 1951). The cortex was stimulated every 30 sec throughout the test. Usually one stimulus was missed when applying or removing a drug. After control responses had been obtained, about 0.015 ml. of saline or distilled water containing the drug in appropriate concentration was delivered onto the filter paper strip. After about 5 min the paper strip was removed from the cortex and stimulation was continued for another 5 to 10 min.

In the other procedure, the strength of stimulation was altered to determine the thresholds for the surface negative response and for the surface positive burst. The drugs were given intravenously or, for ether, by inhalation and the thresholds again determined. The complete test for each drug took about 7 to 10 min. In the initial experiments it was observed that intravenous injection of procaine caused a precipitous fall in the blood pressure. In later experiments the effects of this fall were mitigated by the administration of up to 25 ml./kg of 6.0% dextran in saline.

In both procedures, a minimum of 1 hr was allowed for the effects of one drug to disappear before testing another. The cortical response to direct electrical stimulation was used to confirm the absence of a persistent drug effect.

## RESULTS

*Studies of drug interaction in intact white mice.* Phenobarbitone by itself produced a mild hyperkinesia, followed by ataxia and then loss of the righting reflex if the dose was sufficient. Loss of the righting reflex occurred within 45 min after the intraperitoneal injection of an effective dose of the drug; observation was continued for 60 min after the injection. The dose/response curve for phenobarbitone alone is presented in Figs. 1 and 2 (●).

Both procaine and cinchocaine when given alone produced only signs of central nervous stimulation as indicated by "excitement," hyperkinesia and increased breathing. When convulsions occurred they always were preceded by a period of excitement. In some animals the righting reflex was lost, but only during or following a convulsion. In all mice excitement began within 10 min but was short-lived, seldom lasting longer than 5 min with procaine or 10 min with cinchocaine. If an animal convulsed, death frequently occurred within the ensuing hour. The results obtained with various doses of both drugs are given in Table 1.

When the same doses of procaine were given 60 min after various doses of phenobarbitone, the responses were different. With doses of procaine up to 175 mg/kg following phenobarbitone no excitement or convulsions occurred. Instead,

TABLE 1

CENTRAL NERVOUS STIMULATION FOLLOWING INTRAPERITONEAL ADMINISTRATION OF PROCAINE AND CINCHOCAINE INTO MICE

Ten animals were tested with each dose

| Drug | Dose (mg/kg) | No. of mice exhibiting | |
|---|---|---|---|
| | | Excitement | Convulsions |
| Procaine hydrochloride | 100 | 1 | 0 |
| | 125 | 4 | 0 |
| | 150 | 7 | 1 |
| | 175 | 9 | 3 |
| | 200 | 10 | 10 |
| Cinchocaine hydrochloride | 10 | 1 | 0 |
| | 15 | 5 | 1 |
| | 20 | 8 | 5 |
| | 25 | 10 | 7 |
| | 30 | 10 | 10 |

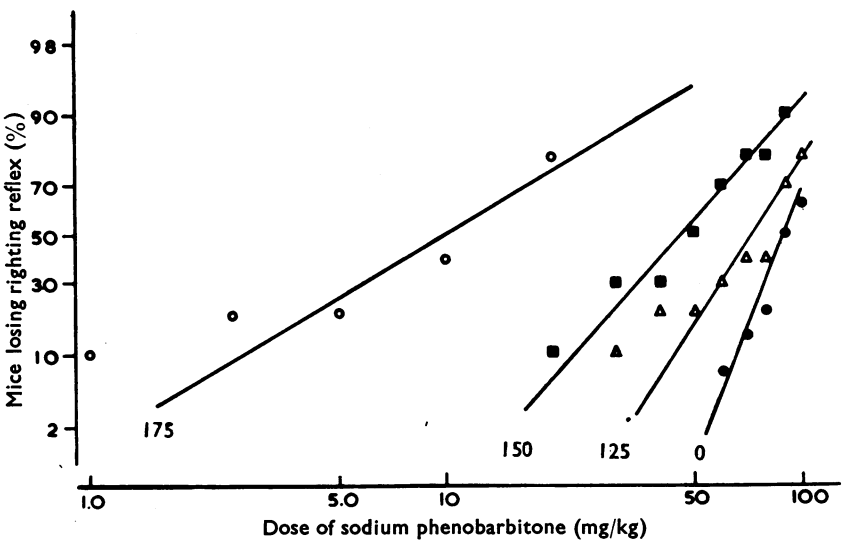


Fig. 1. Loss of righting reflex produced by various doses of procaine given to white mice 60 min after various doses of phenobarbitone. Logarithmic probability plots. Each point is the mean for ten to fifteen mice. Values on graph give doses of procaine (in mg/kg) for each symbol and line.

there was central nervous depression which was assessed quantitatively from the loss of the righting reflex in many of the animals in which it had not been abolished by phenobarbitone. These results have been plotted in Fig. 1.

Statistical comparisons of these curves were difficult because only the curves for 125 and 150 mg/kg or procaine did not deviate significantly from parallelism to each other. In this instance it could be shown that a significantly smaller dose of phenobarbitone was needed to abolish the righting reflex in 50% of the mice following the 150 mg/kg dose of procaine. Similar tests were carried out using 200 mg/kg of procaine, but satisfactory dose/response curves could not be obtained because with very small doses of phenobarbitone the results became erratic and

with higher doses all animals were depressed (100% effect). Procaine (100 mg/kg) abolished the righting reflex in a few animals not previously affected by phenobarbitone, but the effect of this dose was small.

When cinchocaine was given 60 min after various doses of phenobarbitone (Fig. 2), the results were similar to those obtained with procaine; that is cinchocaine inhibited the righting reflex without preceding or concomitant convulsions. However, when the doses of phenobarbitone used for prior treatment were less than 70 mg/kg, the animals exhibited brief intermittent periods of kicking while lying on their sides, after having lost the righting reflex. With cinchocaine (25 mg/kg) and lower subanaesthetic doses of phenobarbitone several animals convulsed either before or following loss of the righting reflex. These animals have not been included

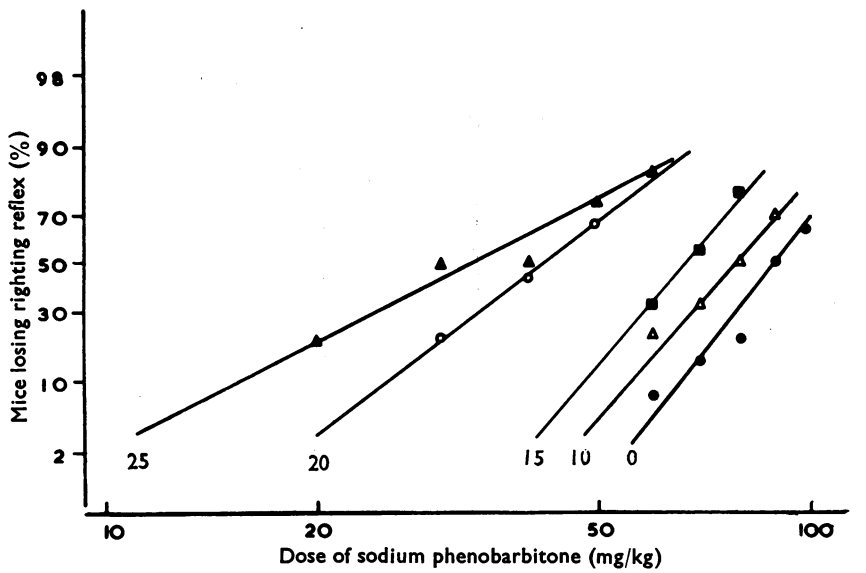


Fig. 2. Loss of righting reflex produced by various doses of cinchocaine given to white mice 60 min after various doses of phenobarbitone. Logarithmic probability plots. Each point is the mean for ten to twenty mice. Values on graph give doses of cinchocaine (in mg/kg) for each symbol and line.

in the results presented in Fig. 2. All the other animals showed ataxia and increased motor activity and many lost their righting reflex. Statistical comparisons showed that the curves for 10 and 15 mg/kg of cinchocaine did not deviate significantly from parallelism with the curve for phenobarbitone alone.

Neither procaine nor cinchocaine restored the righting reflex in an animal previously depressed by phenobarbitone. Procaine (200 mg/kg) or cinchocaine (25 mg/kg) intensified the depression produced by anaesthetic doses of phenobarbitone (120 mg/kg), and usually caused death due to paralysis of breathing. Saline injections in place of the local anaesthetics produced no effect. In some preliminary experiments leptazol (75 mg/kg) restored the righting reflex within 10 min in animals depressed by phenobarbitone, and in very similar experiments Sanders & Halliday

(1962) observed that leptazol antagonized the anaesthetic effect of thiopentone and hexobarbitone.

*Studies of drug effects on isolated slabs of cat cerebral cortex.* The effect of direct application by means of a filter paper strip of procaine (1.5% w/v) and pentobarbitone (3.5% w/v) on the response to direct electrical stimulation of the slab of the cerebral cortex was different from that of leptazol (0.75% w/v). Fig. 3A shows the large surface negative response followed by a surface positive burst obtained with the chosen stimulus strength before the application of the drugs. Procaine and pentobarbitone only decreased the maximum amplitudes of the surface negative and surface positive responses and decreased the duration of the surface positive burst. In contrast, leptazol increased all these parameters. A typical response after application of leptatzol is shown in Fig. 3B. Measurements of all

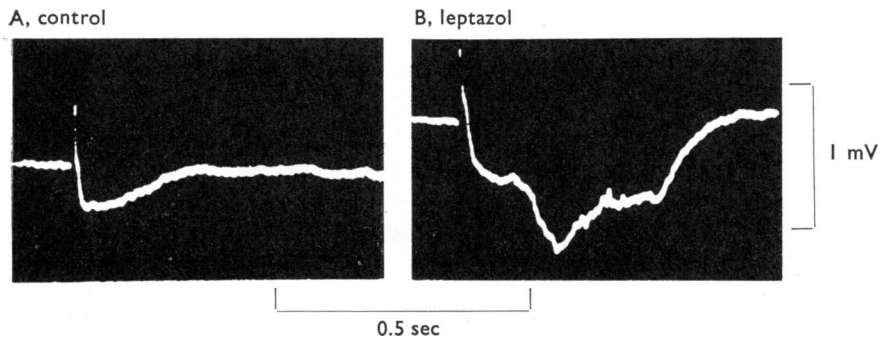


Fig. 3. Effect of the local application of leptazol (0.75% w/v) on the response of a cat's isolated cerebral cortex to direct electrical stimulation with rectangular pulses. There is a surface negative (upwards) followed by a surface positive response. The stimulus artifact is not visible at this sweep speed.

the responses obtained in an experiment of this type on a single cat have been plotted in Fig. 4. This animal was one of five cats tested with all three drugs. Although the details of the plots varied between different animals, the general pattern was the same for all the animals tested ; pentobarbitone and procaine decreased and leptazol increased both responses.

The thresholds for the negative response and for the positive burst were determined before and after parenteral administration of the drugs into eleven cats. When leptazol and procaine, in doses which had previously been shown to produce convulsions in intact and decerebrate cats, were injected intravenously, the threshold for the negative response to direct stimulation of the slab appeared to be unaltered. The same result was obtained when ether was administered at the rate needed to maintain anaesthesia before decerebration. In only two tests, one with ether and one with leptazol, was there a slight decrease in threshold voltage. In about half the tests procaine and ether caused a slight decrease and leptazol a slight increase in the amplitude of the negative response. In the rest the amplitude was not changed.

In contrast the threshold for the positive burst was frequently changed by the drugs. The thresholds were always increased by administration of procaine,

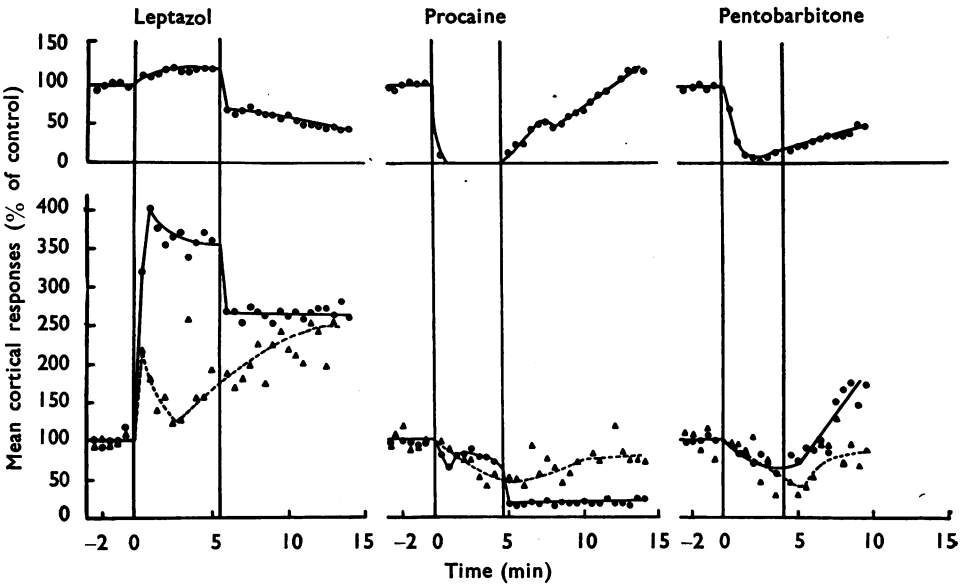


Fig. 4. Effects of local application of leptazol (0.75% w/v), procaine (1.5% w/v) and pentobarbitone (3.5% w/v) on the responses of a cat's isolated cerebral cortex to direct electrical stimulation with rectangular pulses. ○, amplitude of surface negative response; ●, amplitude of surface positive response; △, duration of surface positive response. The cortex was exposed to drugs during the times between vertical lines.

increased or unchanged by ether, and decreased or unchanged by leptazol. The results are given in Table 2. The use of dextran solution in several experiments to mitigate the effects of the large drop in blood pressure which often occurred after intravenous injection of procaine did not greatly modify the results.

TABLE 2

THE EFFECT OF INTRAVENOUS INJECTION OF LEPTAZOL OR PROCAINE OR OF INHALATION OF ETHER ON THE THRESHOLD VOLTAGE REQUIRED TO EVOKE A POSITIVE POTENTIAL IN THE CAT ISOLATED CEREBRAL CORTEX

The responses are expressed as ratios of the voltages required during drug administration compared with a previous control period. * Blood pressure maintained by intravenous administration of dextran solution

| No. of cat | Leptazol (15 mg/kg) | Procaine (30 mg/kg) | Ether |
|---|---|---|---|
| 1 | — | 1·4 | — |
| 2 | — | >2 | — |
| 3 | 0·13 | 16 | 1 |
| 4 | 1 | — | 1 |
| 5 | 1 | 2 | 2 |
| 6 | 1 | 1·6 | 1·3 |
| 7* | 0·8 | 1·3 | — |
| 8* | 0·8 | 2·2 | >2 |
| 9* | 1 | 1·4 | — |
| 10* | 0·8 | 1·4 | — |
| 11* | 0·8 | 1·4 | 1 |

## DISCUSSION

The basic concept underlying the present investigation is that a large number of drugs depress the activity of the vertebrate central nervous system by a common mechanism of action at the cellular level. Further, that this depression is a result of decreased electrical activity or excitability of certain neurones in the central nervous system due to inhibition of the specific increase in sodium conductivity which is responsible for the rising phase of the action potential. The observations that general anaesthetics (Thesleff, 1956 ; Yamaguchi, 1961) and the local anaesthetic procaine (Inoue & Frank, 1962) all suppress electrical activity in frog skeletal muscle fibres by this mechanism led up to this concept and to the present experiments to test it.

Local anaesthetics are not usually considered to depress the central nervous system and neither procaine nor cinchocaine alone can produce general anaesthesia. The explanation proposed here for this apparent contradiction to the above hypothesis is that these local anaesthetics produce an exaggerated form of Stage II of general anaesthesia (Guedel, 1951), and Stage III (or surgical anaesthesia) is not obtained because the higher doses of the local anaesthetics kill the animals either by paralysis of breathing resulting from the excessive central nervous activity or by cardiovascular collapse resulting from the well-known cardiac depressant effects of these agents. The drug interaction studies on intact white mice demonstrated that procaine and cinchocaine could produce a condition indistinguishable from general anaesthesia when given to an animal following the administration of a subanaesthetic dose of a general anaesthetic and that they could not antagonize the central effects of general anaesthetics. The latter finding provides a clear separation between the types of central nervous stimulation produced by analeptic and local anaesthetic drugs.

It would be ideal if drugs could be tested on a localized group of neurones specifically responsible for the maintenance of consciousness. Unfortunately, no such group of neurones is known. The most generally accepted hypothesis assumes that the maintenance of consciousness depends on the overall level of activity of very diverse neurone types located throughout the reticular core of the brain (O'Leary & Coben, 1958). Even though the ideal situation for test was unavailable, it was possible to test whether procaine could depress the electrical activity of some neurones in the central nervous system in a manner similar to the depression produced by general anaesthetics. Since it was expected that low doses of drugs of both types would produce a generalized increase in activity (excitement stage) which probably would mask any direct depression, it was necessary to select for testing a localized system of neurones lacking neuronal connections with the rest of the brain. For convenience the isolated slab of cerebral cortex prepared by the technique of Burns (1951) was used. With this technique, it was shown that procaine and two general anaesthetics depressed the directly-evoked electrical responses of cortical neurones in a similar manner. This depression was evident even when procaine was given systemically at a dose that produced an overall increase in the activity of the central nervous system, as evidenced by excessive motor activity of the cats. Leptazol, which was selected as an example of an analeptic drug, produced opposite changes in the responses of this preparation.

There is much published information which indicates a similarity in the effects of general and local anaesthetics on the central nervous system. First, it should be pointed out that many drugs which can produce local anaesthesia lack a prominent central nervous stimulant effect. For example, many antihistaminic drugs can easily and reliably produce local anaesthesia and also depress the central nervous system (Goodman & Gilman, 1955). On the other hand, as already mentioned, all general anaesthetics can cause central excitation, possibly by suppression of inhibitory neurones, which is called Stage II of general anaesthesia (Guedel, 1951). The classical Stage I is a condition of analgesia. The local anaesthetics procaine and lignocaine produce *analgesia* by an effect on the central nervous system following intravenous administration (Wagers & Smith, 1960). Another central effect produced by both general and local anaesthetics is suppression of experimentally-induced convulsions in laboratory animals and of *grand mal* epileptic seizures in man (Bernhard & Bohm, 1955). Thus, local anaesthetics have a pattern of effects on the central nervous system very similar to the classical pattern of the general anaesthetics.

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