On the Effects of Xylocain on the Central Nervous System with Special Reference to its Influence on Epileptic Phenomena

The cortical electrical after-discharge and the concomittant epileptiform convulsions which follow upon the cessation of a repetitive cortical stimulation have been used in numerous investigations (for review of the classical literature, see MORUZZI[1]) on "experimental epilepsy"[2]. In several reports of recent years, the characteristics of the cortical after-discharge in relation to varying strengths, durations and frequencies of the stimulations, have been described[3]. In connection with our investigations on the corticospinal system in monkeys[4], we also recorded the cortical after-discharge; and, in further investigations on monkeys and cats[5], it was studied under various conditions together with the concomittant ventral root discharges and the changes in spinal reflex excitability. The material offered a basis for a study of the influence of drugs on different central functions with special reference to their effects on the spinal and supraspinal activity during experimental epilepsy. We thereby found that small doses of Xylocain, a well known local anesthetic, evoked characteristic central effects.

When we had established that small intravenous doses of Xylocain blocked the epileptiform cortical after-discharge and the post-stimulatory convulsions, a preliminary investigation was also performed on humans which showed that epileptic fits could be arrested by intravenously injected Xylocain.

The animal experiments were performed on curarized cats in light Nembutal anaesthesia showing a pronounced cortical after-discharge of constant duration. The action potentials were also led off from different nerves and ventral roots during and after the repetitive cortical stimulation and records were made of the mono- and polysynaptic reflexes as well as of the cortical response (area II) to dorsal root stimulation.

Figure 1 *A–F* shows the corticograms led off at one frontal point (tracing *1*) near the stimulating electrode and one parietal point (tracing *2*) remote to the stimulating electrode. The input of the third channel of the EEG apparatus was connected to the L_7 ventral root (tracing *3*) contralateral to the stimulating cortical electrode. Figure 1 *A* shows the normal electrocorticogram (tracing *1* and *2*) before cortical stimulation. The cortex was then stimulated with a train of shocks (frequency 25 per second) during 6 s (records *B* and *C* only show the shock artefacts during stimulation). The following picture (*D*) shows the cortical after-discharge (upper tracings) and the epileptiform outburst in the ventral root (lower tracing) 3 s after the cessation of the repetitive cortical stimulation. Record *E* illustrates the spontaneous cessation of the after-discharge and ventral root outbursts 11 s after the end of the cortical stimulation, and record *F* shows the "post-epileptic" exhaustion or "extinction"[6] (15 s after cessation of stimulation) which, under the standard conditions used, lasted for about 1 min. During the repetitive cortical stimulation, the action potentials were also led off from other ventral roots or nerves (contralateral to the cortical stimulation) and recorded with fast sweep speed on the screen of a cathode ray oscillograph. Records B_1 and C_1 show superimposed records of the action potentials in *N. radialis* which follow upon each stimulus in the train of repetitive cortical shocks, the artefacts of which are seen in *B* and *C* on the continuously running EEG paper. A continuous "tonic" asynchronous discharge is built up during the course of stimulation[2], as seen in record C_1 taken 6 s after the beginning of the repetitive cortical stimulation (*cf.* the steady base lines in record B_1 obtained 2 s after the beginning of the stimulation). The records also show how each cortical shock is followed by a potential response, the latency of which shortens during the course of the repetitive stimulation[2].

The records in Figure 2 show the typical effect of an intravenous injection of 2 mg Xylocain per kg (1% solution), which dose was shown to have no effect on the blood pressure. The drug did not change the spontaneous EEG (2 *A*). The asynchronous "tonic" motoneurone discharge was abolished, and there was no shortening of the latency of the nerve response to each cortical shock (see Fig. 2 B_1 and C_1). The cortical epileptiform after discharge and the concomittant ventral root outbursts were totally abolished (2 *D* and *E*) and the "extinction" was less (2 *F*) than before the administration of Xylocain (1 *F*).

In several experiments, the effect was followed for 60–80 min after the injection of varying doses of Xylocain. In Figure 3 the duration of the epileptiform "post-stimulatory" cortical after-discharge is plotted as per cent of the average pre-injection value (vertical axis) against time from the moment of injection (horizontal axis). The values plotted represent average values from 6 experiments in which doses of 1 mg per kg (open circles) and 2 mg Xylocain per kg (filled circles) were tested. The crosses show the duration values of the after-discharge in the untreated preparation throughout one hour. In accordance with the observation on the abolition of the facilitatory ("latencyshortening") effect of the cortical stimulation on the motoneuron response in *N. radialis* to cortical stimulation (Fig. 2 B_1 and C_1), it was also found that the pronounced facilitation of the monosynaptic reflex, which lasts some seconds after a conditioning repetitive cortical stimulation[3], was totaly abolished by 2 mg Xylocain per kg (for further description of the effect see BERNHARD and BOHM[3].

In comparison with the pronounced central Xylocain effects described, the influence on the spinal reflexes is relatively weak. The same doses of the drug were tested and the graph in Figure 4 shows the influence of 2 mg Xylocain per kg on the duration of the cortical after-discharge (filled circles), the amplitudes of the monosynaptic (crosses) and polysynaptic L_7 ventral root reflexes (open circles). When there was a complete abolition of the epileptiform phenomena during the first 15 min after the injection, the two types of reflexes were only reduced to 65–75%. The reduction of the reflexes could be followed by a transient increase, and this cyclic effect could also be found in spinal, non-anaesthetised preparations. Finally, the rectangles in Figure 4 give

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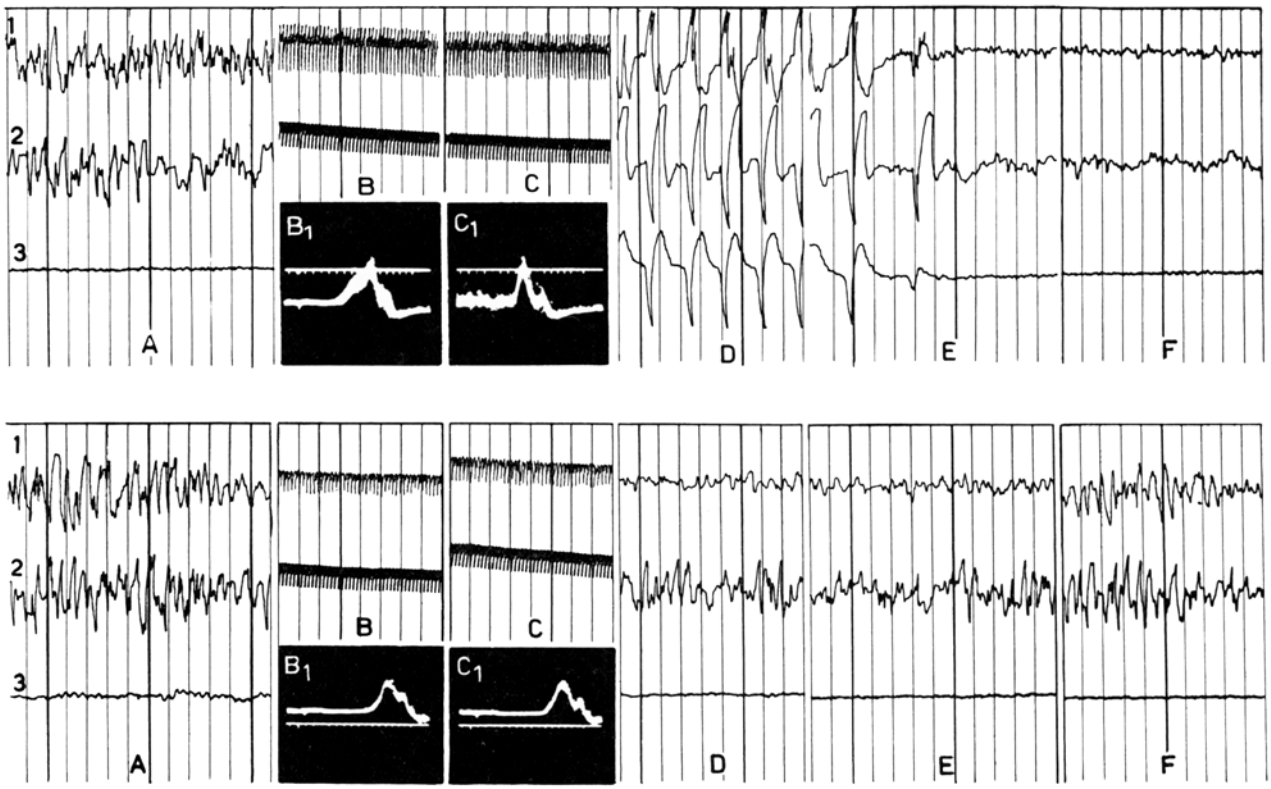


Fig. 1 and 2.–A Comparison of Figure 1 and 2 shows the disappearance of the tonic asynchronous discharge in a peripheral nerve (N. radialis) during cortical stimulation (B_1 and C_1) and the abolition of the epileptiform cortical after-discharge and ventral root outbursts after cortical stimulation (D and E). The records in Figure 1 were obtained before, and those in Figure 2 after intravenous injection of 2 mg Xylocain per kg. Time in A–F in seconds and $^1/_5$ s and in B_1 and C_1 in ms. For further description see text.

the amplitude values of the surface positive cortical response (area II) to single dorsal root stimulation, which response, as can be seen, was not influenced. It should also be mentioned that in some experiments the effect of Xylocain on the cortical after-discharge was compared with that of nembutal and phenemal. In the few experiments which were hitherto carried out, an intravenous injection of 1 mg per kg of Xylocain was 2–3 times more effective than 3 mg phenemal per kg and 5 mg nembutal per kg.

On the basis of the animal experiments, the effect of Xylocain was tested on 5 patients with different types of epilepsy. In investigations on three cases, 6 sustained epileptic attacks (5 of grand mal type and 1 of Jacksonian type) were arrested by intravenous injection of 0·8–1·2 mg Xylocain per kg in the course of the attack (latency for effect 20–40 s). In the treated cases with major epileptic fits, the jerks did not decrease successively but suddenly stopped. In one case with pronounced postictal chewing and salivation which regularly occured after every fit, these phenomena did not occur when the attacks were arrested with Xylocain. In the case of the post-operative Jacksonian epilepsy, following removal of a parietal tumor cyst, the jerks did not disappear after ordinary treatment with barbiturates given intravenously. When the attacks had lasted for three hours, Xylocain was given and the attacks were arrested within

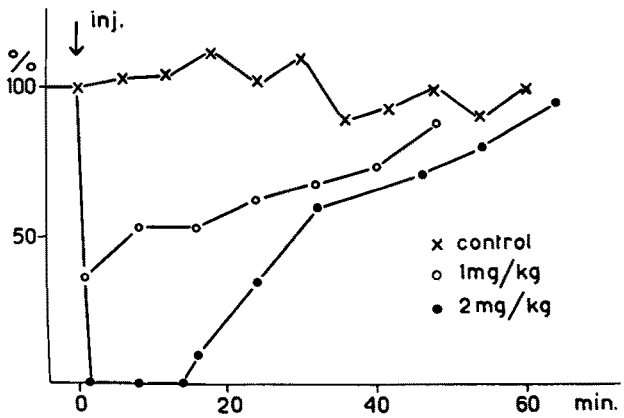


Fig. 3.–Effect of intravenous injection of 1 and 2 mg Xylocain per kg on the duration of the cortical after-discharge (see text).

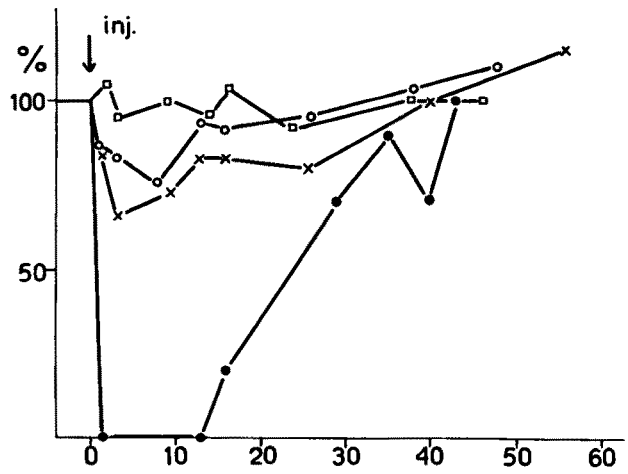


Fig. 4.–Effect of intravenous injection of 2 mg Xylocain per kg on the duration of the cortical after-discharge (filled circles) the amplitude of the mono (crosses) and polysynaptic (open circles) reflexes, and on the amplitude of the surface positive cortical area II response to dorsal root stimulation.

30 s and did not return. One case of *status epilepticus*, following partial removal of the left temporal lobe, did not respond to large doses of barbiturates. However, during the continuous intravenous administration of 0·7 mg Xylocain per kg per hour during 12 h, the attacks successively diminished. After this treatment, the patient could talk which she had not been able to do since the attacks started 3 days after the operation. Finally in one other patient with frequent (4–6 min intervals) fits of short duration (5–20 s), the fits were temporarily abolished. The duration of the Xylocain effect corresponded to the results from the animal experiments.

Further experiments are carried out in order to elucidate the central effects of Xylocain and related compounds; and it should be pointed out that intravenous injections, in connection with convulsions or other motor disorders, must be made with great care until more is known about the central effects of the drug.

C. G. BERNHARD and E. BOHM

Physiological Department II, Karolinska Institutet and Neurotraumatological Clinic, Serafimerlasarettet, Stockholm, May 26, 1954.

Zusammenfassung

Es hat sich gezeigt, dass kleine intravenöse Dosen von Xylocain im Versuch an der Katze die zentralen epileptiformen Nachentladungen und die poststimulatorischen Krämpfe blockieren können, und in Analogie hierzu zeigte eine preliminäre Untersuchung am Menschen, dass epileptische Anfälle durch intravenöse Injektionen von Xylocain abgebrochen werden können.

Informations - Informationen - Informazioni - Notes

STUDIORUM PROGRESSUS

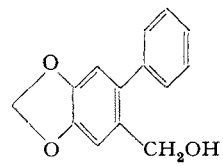
The Structure of Tazettine

By E. WENKERT[1], Ames, Iowa

The chemistry of tazettine, a minor alkaloid of the *Amaryllidaceae*, was investigated first by SPÄTH[2], who had isolated the natural product from the bulbs of *Narcissus tazetta L.* The compound was found to contain a tertiary nitrogen, a methylenedioxy, a hydroxy, and one methoxy functions. Zinc dust distillation yielded phenanthridine, while permanganate oxidation produced hydrastic and oxalic acids. HOFFMAN degradation led to an oily methine base, with an apparent loss of the methoxy group, which could be oxidized with permanganate to a mixture of benzoic and oxalic acids. A two-stage HOFFMAN degradation, however, yielded a crystalline non-nitrogenous compound which was identical with synthetic 6-phenylpiperonyl alcohol (I). On the basis of mainly these experimental results SPÄTH suggested part structure II for tazettine.

In 1936 a direct comparison of tazettine with KONDO's "base VIII"[3], one of the minor alkaloids isolated from *Lycoris radiata Herb.*[4], and with ungernine[5], obtained by ORECHOFF from the bulbs of *Ungernia Sewertzowii (Rgl.)* FEDSCH[6], established the identity of the three compounds. ORECHOFF's few experiments[6] supplemented those of SPÄTH. Thus the hydrogenatibility of the alkaloid pointed definitely to the presence of unsaturation in the molecule, while the isolation of compound I both from a single-stage HOFFMAN degradation and from a vigorous base treatment of the alkaloid itself indicated the general lability of the natural product toward alkali.

In a recent series of six papers, KONDO and coworkers described further structure studies on tazettine*. The alkaloid was found to contain a N-methyl but no C-methyl group, and on HOFFMAN degradation, preceded by methylation, yielded a host of mainly non-nitrogenous products (see Table I), including 6-phenylpiperonyl alcohol (I)*[a,b,e]. Whereas none of the structures of these



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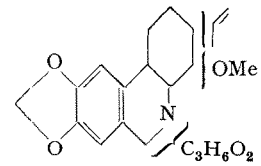

II

"des-N-bases" was known, formulas III and IV were proposed for compounds *A* and *F* respectively*[c,d]. However the synthesis of the methyl ether IV and its non-identity with the hydrogenation product *F* disproved the latter formulation*[d]. Permanganate oxidation of the major "des-N-base" *D* yielded a mixture of the substituted benzaldehyde V and benzoic acid VI which were identical with synthetic specimens*[e]. However a consequent structural assignment VII for the "des-N-base" proved to be also incorrect due to its non-identity with the synthetic product*[f]. Thus while KONDO had previously proposed structure VIII, or its two ketol isomers, for tazettine*[b,c],–a structure which in reality was inadmissible on the basis of the simplest qualitative data, e.g. negative aldehyde and ketone tests,–much of the degradation work appeared to be of little interpretive value.

Most recently a biogenetic scheme encompassing the alkaloids of the *Amaryllidaceae* has been proposed, wherein the possible origin of the basic carbon-nitrogen skeleton of lycorine (IX), the major alkaloid of this family, was presented[1]. An oxidative variation of this biogenesis[2] would lead to structures such as X, requiring a two-carbon side-chain at C–1 of the phenanthridine nucleus,–a requirement borne out by the structures of lycorenine and lycoramine, two minor alkaloids of this series, but violated by the SPÄTH or KONDO

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