Interference with directed movement in the absence of a coincident effect on random mobility as seen at 10% halothane suggests depression of microtubule function without a concurrent effect on the actomyosin microfilament system. At extremely high concentrations (> 20%), halothane probably interferes with both microtubule and microfilament systems resulting in complete paralysis of movement. Although no effect on phagocytosis has been observed at lower concentrations (0.5–2.5%) of halothane[20], total immobilization observed at higher concentrations (> 20%) should be associated with impaired phagocytosis. However, no data are available concerning this possibility.

It has been suggested that the negative inotropic effect of halothane on cardiac muscle is the result of inhibition of ATP utilization by the actomyosin contractile system[23]. A similar effect on neutrophil actomyosin ATP utilization could explain the immobilization observed with high concentrations of halothane. It is concluded that clinically significant concentrations of halothane do not effect neutrophil movement in vitro. Higher concentrations sequentially effect chemotactic and random movement.

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The local anesthetic potency of norcocaine, a metabolite of cocaine

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Summary. The local anesthetic effects of cocaine and one of its main metabolites norcocaine, were investigated comparatively on isolated ganglion cells of the marine gastropod, *Aplysia californica*. During a 1-hour-period, different action potential parameters such as amplitude, duration, maximum rate of rise were observed, which demonstrated that norcocaine exhibits a higher local anesthetic potency than cocaine.

Previous experiments have demonstrated a rapid onset of cocaine *N*-demethylation after cocaine is administered in vivo, suggesting the formation of norcocaine as a cocaine metabolite[2]. Recently norcocaine was found to be present in plasma, brain and cerebrospinal fluid of monkeys in considerable concentrations after intraperitoneal cocaine injection[3,4]. In previous reports, the pharmacological activity of cocaine and norcocaine was examined comparatively. Norcocaine inhibited the cardiac response to tyramine more actively than cocaine[4] and both drugs inhibited the uptake of ^{3}H-noradrenaline by rat brain synaptosomes similarly[3]. On the frog sciatic nerve, norcocaine seemed to cause more local anesthetic activity than cocaine[4]. For a detailed comparative analysis of the local anesthetic potencies of cocaine and norcocaine, the ganglion cells of a mollusc, *Aplysia californica*, were used for the experiments. This preparation permits intracellular recording for periods of hours allowing both compounds to be tested on the same neuron under controlled conditions.

Materials and methods. The dissected visceral ganglion of the marine gastropod was placed into a perfusion chamber. Cells identified according to the nomenclature of FRAZIER et al.[5] were penetrated by micropipettes which were filled with 2 *M* potassium citrate having an electrical resistance of 8–15 MΩ. Standard intracellular recording techniques were used.

Artificial seawater (pH = 8.2) was used as perfusate containing cocaine and norcocaine in a concentration of 10 m*M*. This concentration is lower than the effective dosage for local anesthesia[6,7]; however, it was sufficiently effective to reduce inward current dependent voltage changes. The substances were examined in 7 experiments. In each experiment the effect of cocaine and norcocaine was studied on the same cell. Between each drug application, the ganglion was rinsed for at least 2 hours with artificial sea water, until the action potential parameters recovered to at least 90% of the control values measured at the beginning of the experiment. Furthermore, the sequence of drug examination was changed in each subsequent experiment to eliminate effects dependent upon the sequence of drug administration. Drug applications lasted for 60 min and action potential records were made at 30 and 60 min. Both a conventional display of the action potential (V/t) and a phase plane, i.e. the display of voltage against the first derivative of the action potential (dV/dt) on an X–Y-oscilloscope, were recorded. Cocaine HCl was purchased from E. Merck (Darmstadt,

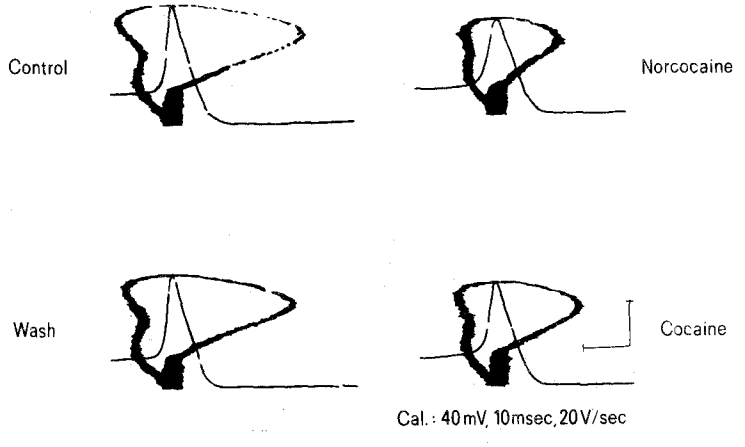

Fig. 1. Influence of a 10 m*M* concentration of cocaine and norcocaine on the action potential and the phase plane of the ganglion cell R-2 of the marine gastropod *Aplysia californica* after 1 h drug contact. Norcocaine revealed a higher local anesthetic potency than cocaine. Note the almost complete recovery of the control action potential after a 2-h-period of washing.

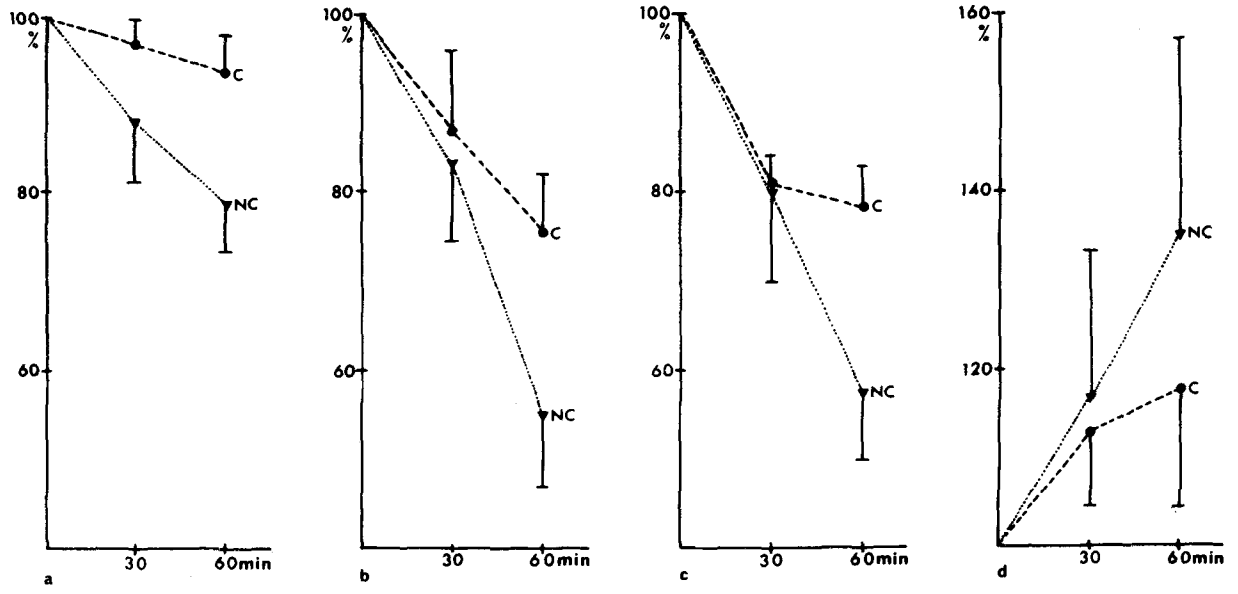

Fig. 2. Effect of cocaine and norcocaine on different action potential parameters. The values were obtained from 7 experiments on the cells R-2(3), R-15(2), L-2(1) and LD(1). *a* Reduction of total action potential amplitude. *b* Reduction of positive peak of the differentiated action potential (dV/dt) i.e. the right hand peak of the phase plane, indicating the inward current. *c* Reduction of the first negative peak of the differentiated action potential i.e. the first or top left hand peak of the phase plane, indicating the inactivation of inward current. *d* Increase of the duration of the action potential measured at one third of total amplitude. All control values were taken as 100%. Standard deviations which are by definitions to plus and minus are drawn to one side only and are represented by the bars.

BRD) and norcocaine HCl was synthesized as recently described[8].

Results. After a 30-min-period of perfusion with cocaine and with norcocaine, spike amplitude, spike duration and maximum rate of rise were markedly decreased. This effect was more apparent with norcocaine than with cocaine. Figure 1 shows both the action potential and the phase plane of one experiment with the cell R-2 after 60 min perfusion with solutions containing cocaine and norcocaine, respectively. The time dependent course of the action potential parameter changes under the influence of the drugs is demonstrated in Figure 2. The change of the parameters is expressed in percent of the control values. The spike duration was measured at one-third of the height of the total amplitude (including overshoot and after hyperpolarization). The rate of rise is equal to the first derivative of voltage as determined by an analog differentiator. The amplitude of the action potential, its maximum rate of rise, and the first maximum of the slope are more strongly influenced by norcocaine than by cocaine. This holds for the spike duration also.

Discussion. The main action of local anesthetics is their interference with the transient increase of cell membrane permeability to the ions carrying the inward current[9]. This effect is expressed by the reduction of the maximum rate of rise of the action potential. This reduction of the inward current is indicated by the decrease of dV/dt during the rise of the action potential, displayed by the deviation on the right-hand side of the phase plane (Figure 1 and Figure 2b). The first and second maximum of the phase plane slope during the falling phase of the action potential, displayed on the left-hand side of the phase plane, are correlated to the inward current inactivation and outward current activation, respectively. The correlation is based upon purely theoretical grounds (W. Daunicht and M. R. Klee, personal communication). This could explain why both drugs reduce the first maximum of the action potential slope, which is correlated to the inward current mechanism, whereas the second maximum, correlated to the outward current mechanism, is not influenced uniformly.

The different parameters of the action potential measured after the drug application indicate that norcocaine interferes to a greater extent with the transient permeability changes of the membrane for inward current carrying ions than cocaine does. This local anesthetic effect is demonstrated especially by the significant reduction of the spike amplitude, the rate of spike rise and the first maximum of the action potential slope. In various preparations, cocaine exhibits its local anesthetic effect on the inside of the membrane[10]. Therefore it can be assumed that the compounds have to penetrate the membrane of the *Aplysia* neurons. 2 explanations seem to be possible for the different local anesthetic potency of cocaine and norcocaine: 1. The *N*-demethylation makes the norcocaine molecule more effective on its site of action, or 2. the different pK-values (cocaine pK = 8.4, norcocaine pK = 8.0, 25 °C) and/or the different lipophilicity enables the 2 compounds to penetrate the cell membrane differently.

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