Structure/Nerve Membrane Effect Relationships of Some Local Anaesthetics

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Abstract. Data on electron structure and octanol-water partition coefficients of certain local anaesthetics are compared with the capacity of reversibly block the action potential of the frog sciatic nerve. Some active parts in the molecules of these substances have been shown to be primarily involved in the action of local anaesthetics.

Key words: Local anaesthetics — Nerve membrane — Partition coefficient — Molecular orbitals

Introduction

Mechanisms underlying the action potential of the nerve membrane are ionic currents passing through the selective membrane channels. One of the present major lines of research concerns the molecular mechanisms by which ionic channels operate in excitable membranes (Hille 1978; Vasilescu 1982). Information concerning the nature and structure of these channels can be obtained by studying the action of local anaesthetics on nerve membranes (Seeman 1972; Strichartz 1973; Courtney 1975; Khodorov et al. 1974, 1976; Almers and Cahalan 1977; Hille 1977a, b, 1980; Cahalan 1978; Borchard and Drouin 1980).

Local anaesthetics are drugs which reversibly block sodium channels in nerve membranes (Taylor 1959). Although numerous theories try to explain anaesthesia, the molecular mechanisms in the action of local anaesthetics still remain unclear.

The present work analyses some data on the electron characteristics of the molecules of anaesthetics by comparing their structure with the ability to reversibly block action potential.

Materials and Methods

a) *Capacity of Local Anaesthetics to Reversibly Block Action Potential*

We have studied the action of four local anaesthetics (procaine, lidocaine, tetracaine and benzocaine) on the sciatic nerve of the frog *Rana ridibunda*. The effects of the anaesthetics were estimated by determining standard electrophysiological parameters of the action potential (rheobase, chronaxy,

conduction velocity of nerve impulse), which are modified by various concentrations of local anaesthetics: this allows to assess the ability of these substances to block action potential. Different concentrations of local anaesthetics in Ringer physiological solution at pH = 7.4 were used. The solution contained (in mol/l): 110×10^{-3} NaCl; 2.5×10^{-3} KCl; 1.8×10^{-3} $CaCl_2 \cdot 2\ H_2O$; 4.5×10^{-3} TRIS-Cl. The pH of the solution of local anaesthetics in Ringer solution was adjusted to 7.4 with NaOH and checked using a Beckman pH-meter. The concentration of local anaesthetic which induced a reversible block of action potential was taken as the threshold dose. The threshold doses obtained are listed in Table 1.

Our data obtained by this method are in a good agreement with those reported by Strichartz (1976).

b) Lipid/Phase/Water Partition of Local Anaesthetics

The physiological activity of local anaesthetics depends on their ability to pass through the lipid membrane barrier (Singer 1980); a good measure of this ability is the partition coefficient (P).

The Hansch fragment method was used to calculate the octanol/water partition coefficients of the four local anaesthetics studied. The values obtained are shown in Table 2. It can be seen that the

Table 1. Relative potencies of some local anaesthetics

Drug	Threshold dose (reversible block of action potential) (mol/l)	Effective* concentration (mol/l)	Z_N (for N atom bound to aromatic ring)
Lidocaine	0.2	0.2 0.25	0.4458
Tetracaine	0.25	—	0.4168
Procaine	0.25	0.25	0.3001
Benzocaine	0.5	0.5 0.8	0.3001

* *Effective concentrations were obtained by evaluating the sodium permeability of Ranvier node* of frog sciatic nerve under voltage-clamp reduced by 50 per cent (Strichartz 1976).

Table 2. Octanol/water partition coefficients of some local anaesthetics

Molecule	log P			
	Neutral form		Protonated form	
	Experimental	Computed	Experimental	Computed
Procaine	0.16 (pH = 7.3)	1.74	−2.24 (pH = 3.8)	−2.26
Benzocaine	1.93[1] (pH = 7.4)	1.42	—	—
Tetracaine	4.25[2] (pH = 7.4)	4.10	2.67[2]	0.10
Lidocaine	3.24[2]	3.77	0.08[2]	0.14

1) Hansch and Leo (1979)
2) Reduced to octanol/water partition according to: Leo et al. (1971)

fragment method reflects in a rather exact way pH-dependent variations of partition coefficients. At standard temperature (25 °C) the neutral anaesthetics are strongly hydrophobic. Actually, temperature has only negligible effects on P when mutually weakly miscible solvents are used, such as n-octanol and water. Results obtained with a variety of solutes in different solvent systems have shown that the effect usually is of the order of 0.01 log/unit/deg. (Leo et al. 1971).

c) Electron Characteristics of Local Anaesthetics

A self-consistent-technique, computation of the Hückel π molecular orbital, was used to compare our experimental data concerning the action of local anaesthetics on the peripheral nerve with their electron structures. The chemical structure of the drugs studied is shown in Fig. 1.

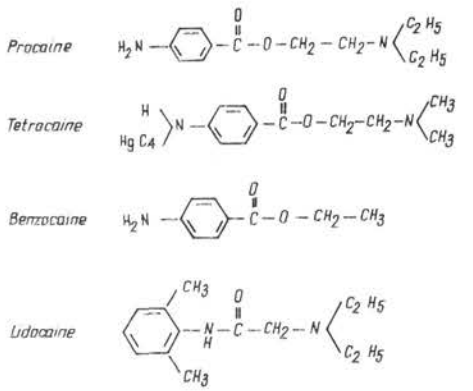

Fig. 1. Chemical structure of some local anaesthetics.

Following input parameters were used: $h_o = 1$; $h_o = 2$; $h_N = 1.5$ (for tetracaine $h_N = 1$); $h_{C-CH_3} = 0.5$; $k_{NC} = 1$; $k_{C=O} = 1$; $k_{C-O} = 0.8$ with a self-consistency up to 1 % in total energy in each case.

Following molecular parameters were calculated: charge densities (q), double bond order (p), free valence (F) (Fig. 2).

Discussion

Computation of π molecular orbitals of the anaesthetics studied provided some data on their structural characteristics which could be compared with those concerning their threshold effects and partition coefficients. The highest value of this parameter was obtained for the aromatic N charge in lidocaine ($Z_N = 0.4458$), an intermediary value for tetracaine ($Z_N = 0.4168$) and a lower value for procaine and benzocaine ($Z_N = 0.3001$).

The results of our comparative study can be summarized as follows:

1. Aromatic nitrogen charge seems to be the major component responsible for the local anaesthetic activity.

2. The presence of a second amino-group in the structure of the molecule of

the anaesthetic raises its activity. This may be explained by the co-operative effects between nitrogen atoms. The co-operative effect of the second nitrogen atom increases the anaesthetic activity with the increase being proportionally inverse to the distance of the atom from the aromatic nitrogen atom. The lowest threshold dose was found for lidocaine which has its amino group closer to the aromatic nitrogen (see Fig. 1).

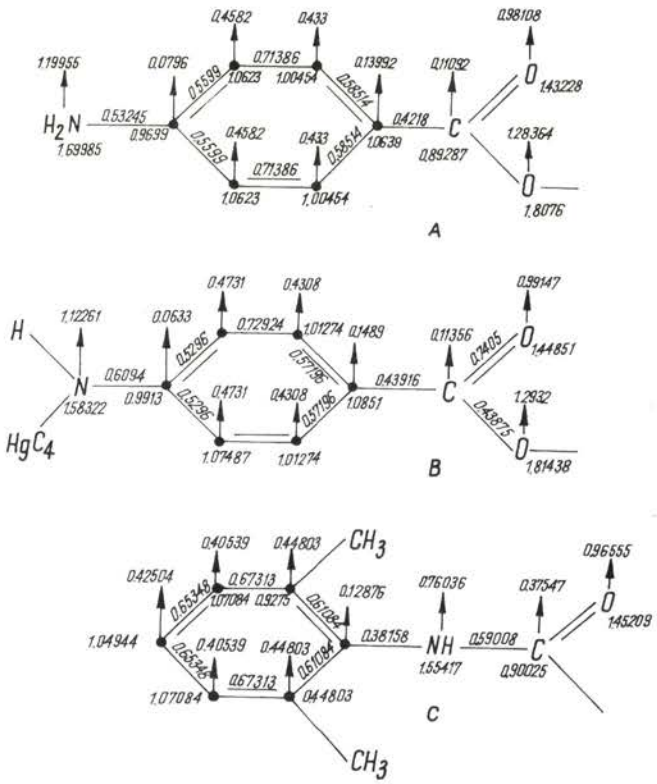

Fig. 2. Molecular parameters (q_i, p_{ij} and F_i) computed for local anaesthetics: *A*) procaine and benzocaine; *B*) tetracaine; *C*) lidocaine. Values of the parameters are shown near the corresponding atom $i(q_i)$, between the atoms i and $j(P_{ij})$ and indicated by the corresponding arrow (F_i).

Our results suggest that the receptor for local anaesthetics has some functional groups which are able to interact with the aromatic nitrogen atom of these drugs. The aromatic nitrogen seems to induce the anaesthetic phenomenon itself while the second nitrogen atom and the alkyl group seem to determine — by co-operative effects — the intensity of anaesthesia.

3. Lidocaine, the most active one of the local anaesthetics studied, has both

a nitrogen atom bound to the aromatic ring and a hight value of the partition coefficient, indicating its capacity to pass easily from the aqueous to the lipid phase.

As compared to lidocaine, tetracaine with a by one order higher partition coefficient has a higher threshold dose on account of 2 structural parameters (a *N*-butyl group bound to the aromatic nitrogen and a carboxyl instead of carbonyl group); it is less active, probably due to the large distance between the two nitrogen atoms co-operatively participating in the blocking action.

Procaine, with a threshold dose equal to that of tetracaine, has a much smaller partition coefficient than tetracaine. Although the molecules of both drugs show the same distance between the co-operative nitrogen atoms, the aromatic nitrogen atom of procaine is not protected by *N*-butyl group as it is case in tetracaine. Due to this both drugs have equal threshold doses. The protected active centre of tetracaine is counter-balanced by its better partition capacity.

The lowest anaesthetic potential was found for benzocaine which lacks the co-operative effect of the second nitrogen atom, though it has a partition coefficient by two orders higher than does procaine.

4. It is worth mentioning that for the sequence lidocaine-tetracaine-benzocaine the increase in the threshold doses is parallel to the decrease in charge of the nitrogen atom bound to the aromatic ring. Procaine represents an exception due to its easy interaction with the receptor.

5. The sequence of partition coefficients is the same for neutral and protonated forms. We only dealt with neutral forms, administering local anaesthetics in a chloride-water solution. Due to alkaline pH (about 7.35) of the body fluids, chloride is rapidly converted into its neutral form which is able to penetrate the membrane lipid phases.

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