The Effect of Metacaine on the Slow Variation of Peak Sodium Currents in Potential Clamped Ranvier Nodes Following Changes in Holding Potential

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Abstract. The effect of changes in the holding potential on peak sodium currents in isolated myelinated nerve fibres (peak I_{Na}) was investigated with the conventional sodium inactivation being kept at $h_\infty = 1$. In Ringer solution no stationary values of peak I_{Na} could be obtained over the potential range tested. Near the normal resting potential, E_R, peak I_{Na} changed with time clearly even after 10 min. Therefore, the individual values of peak I_{Na} as normalized by peak I_{Na} at E_R and corrected for the unevitable run-down of peak I_{Na} could not serve as measure for stationary values of any membrane parameter. Under metacaine (1 mmol/l) peak I_{Na} changed comparably faster and proved to be less potential dependent as compared to peak I_{Na} of the untreated fibre. The effects observed are not necessarily governed by a specific process located inside the nodal membrane.

Key words: Ranvier nodes — Potential clamp — Holding potential — Metacaine

Introduction

The inactivation of sodium permeability in potential clamped Ranvier nodes has been described satisfactorily well by the time and potential depending variable h which after a potential step and at room temperature reaches different steady-state levels within tens of milliseconds (Frankenhaeuser 1959, 1960). Therefore, within the framework of the Hodgkin-Huxley-Frankenhaeuser formalism the increase of peak sodium currents elicited by constant test pulses for several minutes after starting compensation for the injury current (Koppenhöfer and Vogel 1969) remained obscure. In 1973 however, a so-called slow sodium inactivation process was shown to exist in Ranvier nodes (Peganov et al. 1973)

which varies in a sigmoidal manner with the membrane potential and exponentially with time like h, but with time constants in the 100 ms-range. In corresponding experiments an ultra-slow inactivation was introduced which approached a new steady-state level after a change in holding potential within a few minutes following the formalism of the sum of two exponentials (Fox 1976). The slow inactivation process, however, showed an approximately exponential time course and was found largely independent of the state of the h-system (Brismar 1977).

Apart from slow changes of peak sodium currents in the untreated node a local anaesthetic-dependent sodium inactivation with time constants in the 100 ms-range at room temperature was discovered. Under the action of benzocaine, however, slow sodium inactivation evidently did not develop (Khodorov et al. 1976; Hille 1977).

We tested the effect of a structural isomer of benzocaine, metacaine, on slow changes in peak sodium currents. We tried to interpret the observed effects in terms of morphological structures lying in series with the nodal membrane, thus acting as a diffusion barrier.

Materials and Methods

Preparation and measuring device. Experiments were carried out on single myelinated nerve fibres of the frog (*Rana esculenta*). The dissection procedure employed followed the instructions given by Koppenhöfer and coworkers (1987), and delivered clearly curled axons exhibiting a well preserved reserve length.

Ionic current measurements were carried out by means of a commercially available potential clamp device after Nonner (1969). Membrane currents were corrected for leakage currents (Dodge and Frankenhaeuser 1958) automatically and filtered through a low-pass, fourth order Bessel-filter (-3 dB at 80 kHz). No compensation for the influence of nodal series resistance was employed and no corrections for the low-pass filter properties of the current measuring internode (Schumann et al. 1983) were made.

Nomenclature and calibration. The potential of the compartment of the recording chamber containing the node under investigation was taken for the absolute membrane potential, E, (Wiese and Duchâteau 1984) assuming the voltage drop across the series resistance to be negligibly small. Peak sodium currents, peak I_{Na}, were calculated from the early peak output voltage of the clamp amplifier and the individual fibre dimensions, assuming a specific resistance of the axoplasm of 110 Ωcm (Stämpfli and Hille 1976).

Solutions. The normal bathing medium for the node under investigation was Ringer solution containing (mmol/l): NaCl 112.0; KCl 2.5; $CaCl_2$ 2.0; *tris*(hydroxymethyl)-aminomethane HCl-buffer 2.5; and tetraethylammonium chloride 5.0 for depressing potassium currents (Hille 1967; Koppenhöfer 1967; Schönle and Koppenhöfer 1983). Test solutions were prepared by adding metacaine (1 mmol/l) in substance as the highly water-soluble methanesulfonate of ethyl *m*-aminobenzoate (MS-222®, Sandoz AG, Nürnberg, W. Germany). Note that the anion has proved to be inert and test solutions older than 10 hours were discarded (Sommer et al. 1984). The node under investigation was continuously rinsed by the specific bathing medium. For getting stationary and reversible drug effects current measurements were started after wash-in and corresponding

wash-out time intervals of 1 and 2 min, respectively. The adjacent internodes were cut and immersed in an artificial intracellular fluid (in mmol/l): KCl 108.0; NaCl 10.0; "tris-buffer" 2.5. The pH of all solutions employed was set at 7.2 ± 0.1, and the temperature was kept at 15 ± 0.5 °C.

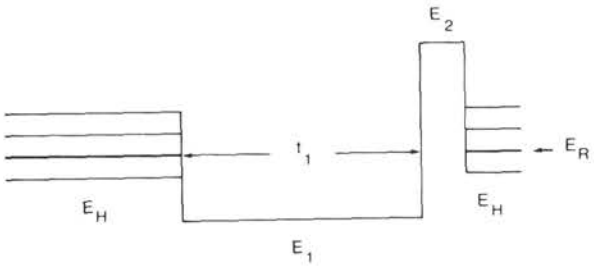

Fig. 1. Pulse program used to investigate the effect of long lasting potential changes on peak sodium currents. Starting from membrane potential, E_R, different values of holding potential, E_H were set. Test pulse amplitude, E_2, was set 60 mV positive and prepulse amplitude, E_1, was set 60 mV negative as related to E_R of individual fibres. Duration of E_1: 50 ms. The diagram is not drawn to scale.

Pulse program. The sequence of membrane potential changes applied to the node is illustrated in Fig. 1. The positive short test pulse E_2 which elicited peak sodium currents, peak I_{Na}, was preceded by a negative prepulse E_1 of the duration $t_1 = 50$ ms which kept the conventional inactivation variable h at $h_\infty = 1$. Following most contemporary experimenters we defined $h_\infty = 0.8$ at rest and measured the resulting holding potential $E_R = -76.2 \pm 3.5$ mV (mean $\pm s$; $n = 9$). Concerning the step width chosen we kept $E_1 = E_R - 60$ mV and $E_2 = E_R + 60$ mV throughout this kind of experiments. Starting from E_R different values of the holding potential, E_H, were achieved by appropriate holding currents for potential steps of 15 mV, first in negative and thereafter in positive direction.

Surprisingly the preparations proved to be sensitive to hyperpolarizing holding currents. As early as at membrane potentials of $E_H = -107$ to -120 mV the holding current became irregular, and in specific axons a final break-through of the membrane was seen already at $E_H = -110$ to -115 mV. No explanation for this finding is known to us so far. However, taking into account that axons showing a well-preserved reserve length exhibit an extraordinary low series resistance (Koppenhöfer et al. 1987) one could argue that a reasonable large series resistance is capable of protecting the nodal membrane in some unknown manner against noxious current densities at strong hyperpolarizing holding currents.

For comparison, changes in peak I_{Na} due to changes in h_∞ were investigated by the conventional two-pulse protocol (Frankenhaeuser 1959).

Results

The well-known effect of hyperpolarizing prepulses E_1 of sufficient length on the inactivation variable h is shown in Fig. 2 (*a*, *b*). Starting from $E_R = -70$ mV and without prepulses ($E_1 = E_R$) peak sodium currents, peak I_{Na}, were elicited by constant test pulses, $E_2 = -10$ mV (*a*). Under metacaine (*B*) peak I_{Na} was markedly and reversibly diminished as compared to peak I_{Na} in normal Ringer

solution (*A*) as has been shown earlier (Sommer et al. 1984). Hyperpolarizing prepulses of $E_1 = -130\,\text{mV}$ and of sufficient length for keeping h at $h_\infty = 1$ at the end of E_1 (*b*) compensated partly for the increased inactivation induced by the application of some derivatives of benzoic acid (Hille 1977; Jedicke et al. 1988; Koppenhöfer et al. 1987). The fact that under metacaine (*B*, *b*) peak I_{Na} remained still smaller than in the untreated fibre (*A*, *b*) has been attributed to a reduction of the permeability constant $\bar{P}_{Na}$ by metacaine (Froese 1986; Jedicke et al. 1988).

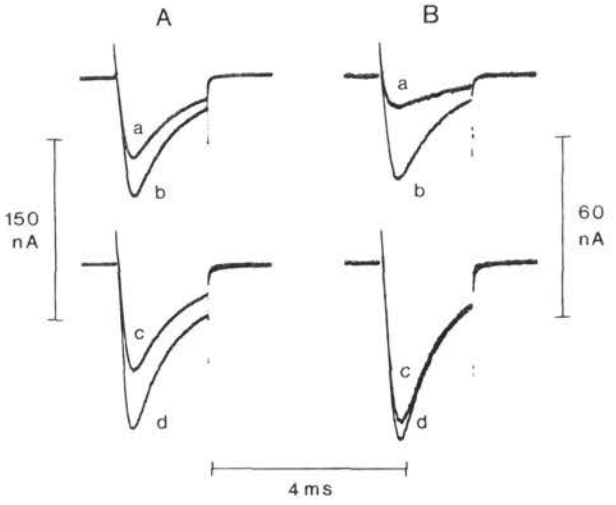

Fig. 2. Peak sodium currents in Ringer solution (*A*) and under the influence of 1 mmol/l metacaine (*B*). Upper records: effects of prepulses of 50 ms in duration at constant holding potentials. *a*: $E_H(=E_R) = E_1 = -70\,\text{mV}$. *b*: $E_H(=E_R) = -70\,\text{mV}$; $E_1 = -130\,\text{mV}$. Lower records: effect of changes in holding potential, E_H, after two minutes and at constant prepulse potentials, $E_1 = -130\,\text{mV}$. *c*: $E_H(=E_R) = -70\,\text{mV}$; *d*: $E_H = -110\,\text{mV}$. Note different current calibration. $E_2 = -10\,\text{mV}$ throughout. The peak values of the initial capacity currents are cut.

In subsequent runs the effect of long lasting changes in holding potential, E_H, on peak sodium currents was investigated (Fig. 2 *c*, *d*). The prepulse potential was kept at $E_1 = -130\,\text{mV}$, thus $h_\infty = 1$ and the test pulse potential was again fixed at $E_2 = -10\,\text{mV}$. Starting from $E_R = -70\,\text{mV}$, peak sodium currents were diminished by metacaine (*B*, *c*) as compared to peak I_{Na} under normal conditions (*A*, *c*) to a lesser extent than in corresponding runs with $E_H = E_R$ at the beginning of the experiment (*b*). It has remained unclear whether this was an unwanted after-effect produced by the long lasting, graded changes in E_H applied in the meantime (the same experiment as in Fig. 4). When the holding potential was lowered to $E_H = -110\,\text{mV}$ (*d*) the peak sodium currents increased

as it was expected from reports on the so-called slow sodium inactivation (see 225, 226). Note that under metacaine (*B*) the increase was less pronounced than in the untreated node (*A*).

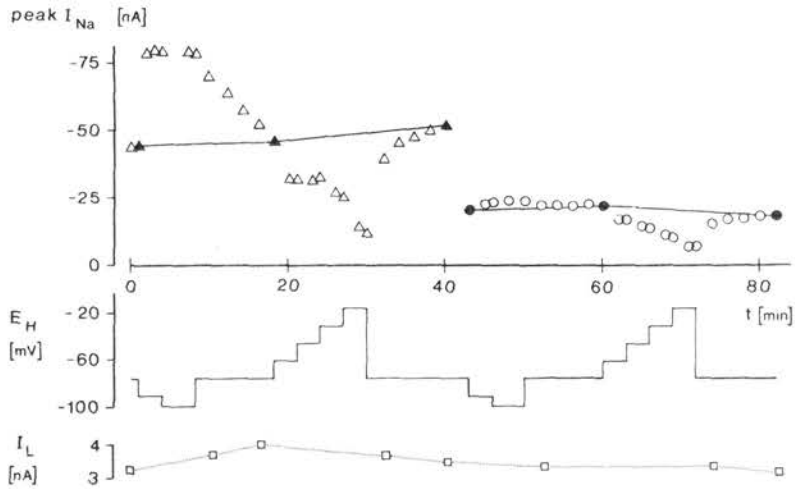

Fig. 3. Changes in peak sodium currents, peak I_{Na}, (upper ordinate) in Ringer solution (triangles) and after administration of 1 mmol/l metacaine (circles) under the influence of changes in holding potential, E_H, (middle ordinate). Filled symbols: quasi-stationary values of peak I_{Na} at $E_R = -77$ mV in Ringer solution (triangles) and under the influence of metacaine (circles). Lower ordinate: leakage currents (squares) as measured at hyperpolarizing potential steps of -40 mV.

The influence of graded changes in holding potential on peak sodium currents is shown on Fig. 3. Starting from E_R, E_H was adjusted first to more negative values, and peak I_{Na} was measured at least two times after the onset of each potential step. As expected from Fig. 2, more negative values of E_H caused an increase in peak I_{Na} up to saturation (maximum peak I_{Na}) at $E_H = -100$ mV in this experiment, both in normal Ringer solution (triangles) and under metacaine (circles). The reduction of maximum peak I_{Na} under metacaine is clearly visible and reflects the metacaine-induced reduction of $\bar{P}_{Na}$ mentioned before. Note that in Ringer solution and at depolarizing holding currents peak I_{Na} did not attain stationary values even after 2 min. Moreover, at $E_H = E_R$ this held for more than 10 min. Under metacaine, however, the measured values represent largely stationary values.

The dotted line in Fig. 3 delineates the time-related change in leakage currents I_L (squares) elicited by constant hyperpolarizing potential steps of -40 mV. Average I_L stood reasonably constant (change: 2.6 %/*h*; $n = 8$) al-

though its value scattered tremendously between individual experiments (standard deviation, $s = 31\ \%$).

The dependence of peak I_{Na} on long lasting changes in E_H, was examined by refering peak I_{Na} to its simultaneous value one would measure if the holding potential were kept at E_R. For this purpose the latest values of peak I_{Na} measured at E_R (filled symbols) were interpolated linearly (solid line) and the latest values of peak I_{Na} measured at various levels of E_H (open symbols) were divided by the simultaneous value of the solid line and plotted versus holding potential E_H (Fig. 4). Peak I_{Na} at E_R in Ringer solution before ($\triangle$) and after ($\triangledown$) application of metacaine were both defined as 100 % (filled triangles).

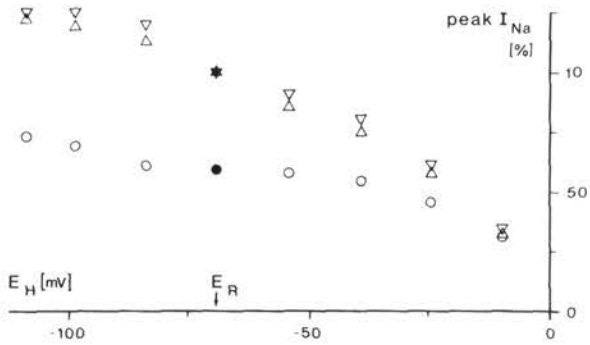

Fig. 4. Effect of changes in holding potential, E_H, on peak sodium currents, peak I_{Na}, after 2 min (open symbols) as normalized to peak I_{Na} at $E_H = E_R = -70$ mV in a specific run (filled symbols). Triangles: prior and after administration of 1 mmol/l metacaine, circles: during the administration. Note that the measured values are scaled to peak $I_{Na} = 100\ \%$ in Ringer solution at $E_H = E_R$. The same experiment as in Fig. 2.

Therefore, in this kind of presentation the inevitable run-down of peak I_{Na} (and its unduly large scatter) as measured in Ringer solution at E_R to $46.6 \pm 42.2\ \%$ ($n = 9$) of its starting value during one run and during three runs to $45.2 \pm 35.4\ \%$ ($n = 8$) is not detectable. Under metacaine and at E_R (filled circles) peak I_{Na} was reduced to $49.8 \pm 18.5\ \%$ ($n = 9$) as related to the mean value of peak I_{Na} at E_R (100 %) of the corresponding runs in Ringer solution; this may be interpreted as blockade of $\bar{P}_{Na}$ as mentioned above.

As it can be seen from Fig. 4 peak I_{Na} increased with more negative values of E_H and saturated clearly; this was also the case under metacaine (circles). Under less negative values of E_H peak I_{Na} decreased but it did not become zero even near zero holding potential. The steepness of the potential dependence of peak I_{Na} was calculated by linear interpolation between the measured values in the potential range of $E_R \pm 20$ mV. In Ringer solution peak I_{Na} changed by $10.2 \pm 7.1\ \%$ per $\Delta E_H = |10|$ mV ($n = 9$). Under metacaine the corresponding

figure ($4.7 \pm 4.4\,\%$; $n = 9$) was significantly smaller (error probability, $\alpha < 0.05$).

Discussion

As expected peak sodium currents elicited by constant test pulses at $h_x = 1$ depend on the holding potential, E_H, applied. In the untreated node approximately stationary values of peak I_{Na} were obtained with hyperpolarizing values of E_H only. Therefore, following the classical Hodgkin-Huxley-Frankenhaeuser formalism it seemed pointless to use peak I_{Na} as measured by the pulse program shown in Fig. 1 for a telling measure for stationary values of any membrane variable governing slow changes in peak I_{Na} following long lasting potential changes as has been done earlier (Brismar 1977; Fox 1976; Peganov et al. 1973). No doubt, the finding that stationary values are not available within practicable time intervals after positive potential steps cannot be explained exclusively by unspecific deteriorations of the nodal membrane because in average the leakage current stood reasonably constant for one to two hours and the concomitant decrease of peak I_{Na} at E_R amounted to less than 50 % only. Moreover, under metacaine and after corresponding potential steps clearly stationary values were obtained.

Contrary to the effect of benzocaine (Hille 1977; Khodorov et al. 1976), under metacaine peak I_{Na} does depend on holding potential although the change is only half as large as in the untreated fibre. The reason for the latter being about one third only of the corresponding value taken from Fig. 6 of Brismar (1977) remained unclear to us.

The classical theory regarding transmembraneous ionic currents (Frankenhaeuser 1968) does not consider the functional meaning of structures in front of the nodal membrane. Consequently, slow changes in peak sodium currents have been attributed exclusively to processes within the nodal membrane (Neumcke et al. 1976). However, considering the huge deficit of settled and detailed knowledge on the functional meaning of the nodal gap structure and in particular on the available amount of sodium ions near the nodal membrane (for references see: Berthold and Rydmark 1983a; Landon and Hall 1976) it seems haste to modify unconstrainedly the Hodgkin-Huxley-Frankenhaeuser formalism by introducing a new membrane parameter (Brismar 1977; Fox 1976; Peganov et al. 1973).

Obviously, the electrical access to the membrane under investigation from the extracellular bulk solution is complicated by electronoptical dense material within the nodal gap (Berthold 1978; Berthold and Rydmark 1983b; Quick and Waxman 1977; Sommer, unpublished). These structures are commonly thought

to represent a considerable diffusion barrier corresponding to an electric resistance of a few hundred kiloohms in series with the nodal membrane in frog nerve fibres (Drouin and Neumcke 1974; Dubois and Bergman 1975; Koppenhöfer et al. 1984; Stämpfli and Uhrík 1980). Changes in potassium concentration underneath the diffusion barrier following positive test pulses of tens of milliseconds have been established (Attwell et al. 1980; Moran et al. 1980). Possibly the increase in sodium concentration at the inside of the nodal membrane resulting from volleys of positive test pulses (Bergman 1970) has something to do with the dependence of peak sodium currents from the holding potential we observed. The fact that peak sodium currents reduced by metacaine are less dependent on holding potential and change faster than stronger currents in the untreated axon might favour this idea.

Assuming the holding current to be carried mainly by potassium ions as it has been claimed for the leakage current (Hille 1973), hyperpolarizing and inward directed holding currents would remove potassium ions from the outside of the nodal membrane and underneath the diffusion barrier mentioned above. The cation exchanger properties of the nodal gap substance (Langley 1979) and in particular, with the ion exchange in the paranodal region (Ellisman et al. 1980; Wiley and Ellisman 1980) in mind, this could promote the flow of sodium ions (maintained at high levels by polyanions in front of the nodal membrane) into the axon, thus explaining the increase in peak I_{Na} seen under hyperpolarizing holding currents. In that case changes in the microenvironment in direct vicinity of the nodal membrane (Lehninger 1968) would be responsible for the slow changes in peak I_{Na} we observed in the present experiments.

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