Short communication

Potassium channel blockers from *Ruta* – a new approach for the treatment of multiple sclerosis

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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with a focal loss of myelin (plaques) which leaves the bared axon cylinder physically intact for quite a long time after the onset of the disease The variety of localization of plaques and the great number of abnormal modes of impulse conduction give rise to the complex functional deficits seen in MS (Waxman 1981) No specific and completely effective agent against MS has been discovered so far (Lauer and Firnhaber 1988)

Demyelination implies uncovering of internodal potassium channels (Chiu and Ritchie 1982) which tend to clamp the axonal membrane potential close to the potassium equilibrium potential, thus rendering impulse propagation difficult (Waxman 1987) Therefore, the role of potassium channel blockers such as 4–aminopyridine (4–AP) in improving impulse conduction in demyelinated axons has received much attention (see e g , Sherrat et al 1980, Targ and Kocsis 1985) Although 4–AP improves different clinical signs in multiple sclerosis, e g latencies of visual evoked potentials and abnormal visual fields, the therapeutic role of 4–AP in long-term treatment of MS is limited by unwanted side effects like paresthesia, dizziness etc (Jones et al 1983, Davis et al 1986, Stefoski et al 1987, 1991, van Diemen et al 1991)

There are unpublished reports from South America of positive effects on MS by long-term treatment with tea made from the medicinal plant *Ruta graveolens* (V Carstens, personal communication) In fact, an infusion of the *Ruta* plant prepared with Ringer solution (containing in mmol/l NaCl 107 0, KCl 2 5, CaCl$_2$ 2 0, N-bis(hydroxyethyl)-2-amino-ethanesulfonic acid/NaOH buffer 5 0) exhibits potassium channel blocker properties (Bohuslavizki et al 1988) This has been tested with isolated myelinated nerve fibres of the toad *Xenopus laevis* by means of an improved version of the so-called potential clamp technique described in detail elsewhere (Bethge et al 1991) Potassium currents, elicited by positive test pulses

(Fig 1 *A*) were reversibly depressed by *Ruta* extract (for preparation see Bethge et al 1991) in a time dependent manner the remaining transient peak value (left arrow) is followed by a comparatively smaller steady state value (right arrow) Note that a concomitant slight reduction of peak sodium currents (*B*, arrow) exists It is not known so far whether this is due to a limited selectivity of the potassium channel blockers under test or to effects of further neuropharmacologically active compounds of the *Ruta* plant (Bautz et al 1990)
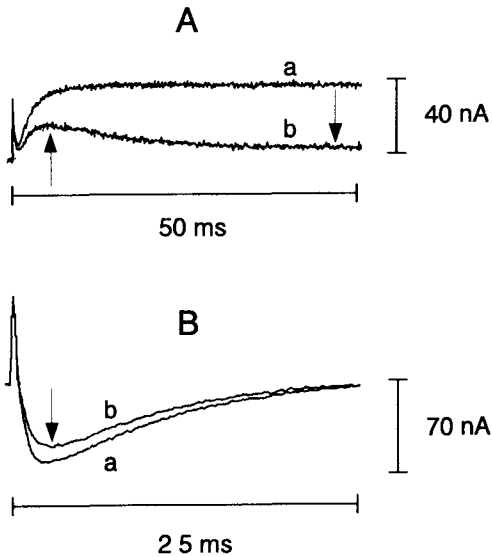

Figure 1. Membrane currents of an intact Ranvier node elicited by rectangular test pulses *A* test potential $E = 80$ mV *B* $E = 0$ mV a Ringer solution, b Ringer solution plus *Ruta* extract corresponding to 2 g plant material/100 ml Temperature 10 °C, pH 7 2

A possible mode of action of potassium channel blockers in demyelinated axons is sketched out in Fig 2 *A* represents the well known saltatory conduction of the nervous impulse (see insets) in the intact myelinated nerve as represented by the delay time $\overline{ab}$ between N_1 and N_2, i e the delay time between the ionic currents generated by N_1 (continuous lines) and the corresponding currents generated by N_2 (dotted lines) *B* represents a demyelinated axon with an abrupt loss af myelin in connection with electron microscopical findings (see, e g Raine 1984, Fig 4) The membrane area to be depolarized by the action currents of N_1 is considerably enlarged and uncovering of many of potassium channels (●) leads to hyperpolariza tion of the denuded membrane areas, thus $|E_R'| > |E_R|$ As a consequence the delay time is markedly increased ($\overline{ac} > \overline{ab}$) or even conduction block occurs (right inset subthreshold response) Note that for simplicity the topical distribution of ionic channels has been assumed to remain constant *C* corresponds *B* morphologically however, most of the potassium channels (●) have been blocked by specific block
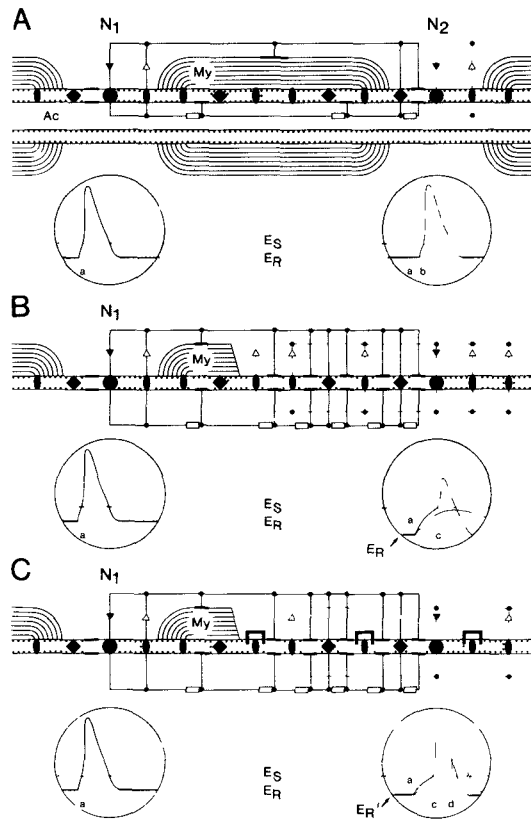
Figure 2. Simplified propagation of the nervous impulse in the intact myelinated axon (*A*) and after demyelination (*B*, *C*) on the basis of ionic currents of the nerve membrane. N_1, N_2: neighbouring Ranvier nodes; *My:* myelin sheath; *Ac:* axon cylinder; ●,◖: sodium and potassium channels, respectively; —▶—, —▷—: sodium and potassium currents, respectively; ◆: leakage currents; ╫: membrane capacity; continuous lines: action currents, generated by N_1; dotted lines: membrane currents, elicited by the action currents N_1. Insets: E_R: normal resting potential; E_R', E_R'': resting potential of the demyelinated axon before and after treatment, respectively; E_S. threshold potential. *A*: normal delay time ($\overline{ab}$). *B*: increased delay time by demyelination, thus $\overline{ac} > \overline{ab}$ and total block, respectively. *C*: improved pulse conduction by potassium channel blockers (⊓), thus $\overline{ac'} < \overline{ac}$, and abnormal delay time $\overline{ad}$ instead of conduction block, respectively. Note that axon-Schwann cell interactions were not taken into account. (From Bautz et al. (1990) with permission of Springer-Verlag, Berlin)

ers (⊓) . Consequently, the demyelination-induced hyperpolarization is diminished ($|E_R''| < |E_R'|$) and propagation of the nervous impulse is improved by shortening

the pathologically increased delay time ($\overline{ac}' < \overline{ac}$). In other words: the so-called conduction safety factor (Tasaki 1953) is increased by pharmacological blocking of pathologically activated potassium channels.

Abnormal visual fields are a paradigm for MS-induced nerve lesions (Davis and Schauf 1981). Therefore, it seemed promising to test the efficacy of potassium channel blockers from *Ruta* in MS patients by a computer-controlled version of profile perimetry (Harms 1960). Threshold measurements were carried out following te so-called up and down method (see, e.g. Bebie et al. 1976) using standard techniques for static quantitative perimetry. In a single-blinded, placebo controlled study nine patients out of 96 patients tested exhibited scotomata of at least 6° in width and of at least 1 dB in depth as compared to normal control subjects of corresponding age. In five cases statistically significant positive effects were observed within about 2 to 4 hours for one or two days after dispensing orally a single dose of an infusion (according to the German Pharmakopoeia No. 8) made of 3 g of the drug (Fig. 3, black areas). In four cases, however, no effects were detectable. This could be due to a different percentage of so-called borderline-axons in individual plaques (Stefoski et al. 1987), i. e. axons with a safety factor just below unity or to unknown pecularities of pharmacokinetics of the drug.
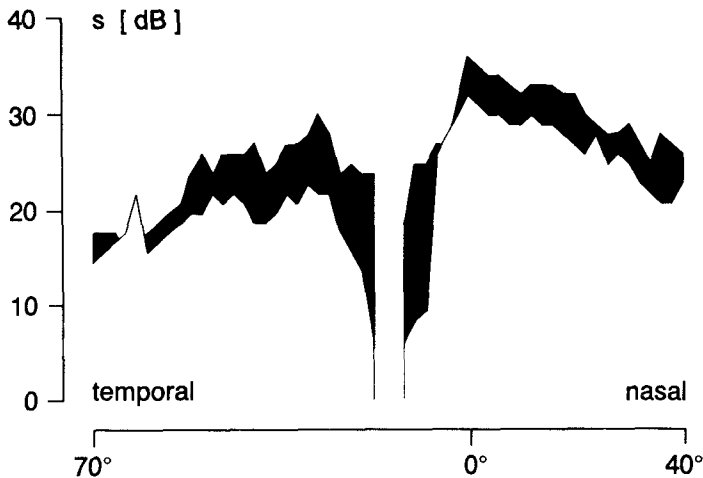

Figure 3. Profile perimetry in an MS-patient with an extensive visual field defect. Abscissa: meridian which hits the blind spot; 0°: fovea centralis. Ordinate: contrast sensitivity, s, in dB; 0 dB = 318.3 cd/m^2 Black areas: improvement of sensitivity 3.5 hours after taking *Ruta* tea. Background luminance: 0.32 cd/m^2. Distance of test points: 2°.

Following the very simplified model shown in Figure 2 potassium channel blockers should act basically in any demyelinated lesion. This is evidently cor-

rect because some patients who tried a long-term treatment with *Ruta* on their own responsibility noticed improved vision and in particular, considerable loss of spasticity some hours after dispensing *Ruta* tea lasting for about one day. It is quite remarkable that under the chosen dosage no unwanted side effects have been reported so far, although *Ruta* contains a considerable number of toxic compounds (Bautz et al. 1990). Nevertheless, for further studies with higher doses and long-term treatment the chemical structure of the active principle of *Ruta* has to be identified. Because a therapy for cure or prevention of MS and related diseases is not yet available as mentioned above a specific symptomatic therapy and largely free of unwanted side effects would fill an urgent need for many patients (Davis and Schauf, 1981).

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