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Research Report

Developmental impairment of compound action potential in the optic nerve of myelin mutant *taiep* rats

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ABSTRACT

The *taiep* rat is a myelin mutant with an initial hypomyelination, followed by a progressive demyelination of the CNS. The neurological correlates start with tremor, followed by ataxia, immobility episodes, epilepsy and paralysis. The optic nerve, an easily-isolable central tract fully myelinated by oligodendrocytes, is a suitable preparation to evaluate the developmental impairment of central myelin. We examined the ontogenic development of optic nerve compound action potentials (CAP) throughout the first 6 months of life of control and *taiep* rats. Control optic nerves (ON) develop CAPs characterized by three waves. Along the first month, the CAPs of *taiep* rats showed a delayed maturation, with lower amplitudes and longer latencies than controls; at P30, the conduction velocity has only a third of the normal value. Later, as demyelination proceeds, the conduction velocity of *taiep* ONs begins to decrease and CAPs undergo a gradual temporal dispersion. CAPs of control and *taiep* showed differences in their pharmacological sensitivity to TEA and 4-AP, two voltage dependent K^+ channel-blockers. As compared with TEA, 4-AP induced a significant increase of the amplitudes and a remarkable broadening of CAPs. After P20, unlike controls, the greater sensitivity to 4-AP exhibited by *taiep* ONs correlates with the detachment and retraction of paranodal loops suggesting that potassium conductances could regulate the excitability as demyelination of CNS axons progresses. It is concluded that the *taiep* rat, a long-lived mutant, provides a useful model to study the consequences of partial demyelination and the mechanisms by which glial cells regulate the molecular organization and excitability of axonal membranes during development and disease.

1. Introduction

The disruption of normal myelination that characterizes myelin mutants provides a useful approach to study the pathophysiology of myelination (Lunn et al., 1995; Baumann and Pham-Dinh, 2001). The *taiep* rat is an autosomic recessive myelin mutant whose name is the acronym for their main neurological symptoms: tremor, ataxia, immobility episodes, epilepsy and paralysis (Holmgren et al., 1989; Duncan et al., 1992). *taiep* rats postnatally develop a severe dysmyelination of

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the CNS, characterized by partial myelination, abnormal periaxonal organization and decompaction of lamellar structure (Lunn et al., 1995, 1997; Krsulovic et al., 1999; O'Connor et al., 2000). Later, these alterations are followed by a progressive demyelination along *taiep* development but with a normal life span. This condition is ascribed to an accumulation of microtubules in the cytoplasm of the oligodendrocytes, impairing the transport of newly synthesized myelin-related proteins or mRNA towards the membrane (Duncan et al., 1992; Couve et al., 1997; Lunn et al., 1997; Krsulovic et al., 1999). In addition, a close association between microtubules (MTs) and endoplasmic reticulum (ER), forming tight MTs–ER complexes that accumulate within oligodendrocyte as the mutants age, interferes with the formation and maintenance of central myelin (Krsulovic et al., 1999). Nevertheless, previous results demonstrated a more severe demyelination in thin myelinated tracts (optic nerve, gracilis dorsal column and corticospinal tract) than thick tracts (ventral columns) (Lunn et al., 1997; Krsulovic et al., 1999), suggesting that not all the oligodendrocytes are affected homogeneously. The functional consequences of demyelination in *taiep* rats have been studied electrophysiologically. Auditory, visual "and somatosensory evoked potentials exhibited delayed or absent central components, without alteration of the peripheral ones (which correlates with the full maintenance of the Schwann cells) (Benítez et al., 1997; Roncagliolo et al., 2000). An immature developmental pattern of monosynaptic reflexes in the spinal cord, explained in part by the demyelination of the central component of the reflex circuit, has been recently reported (Fuenzalida et al., 2004). These electrophysiological findings can be accounted for, at least in part, by alterations of the conduction properties of myelinated fibers in central tracts, due to demyelination-induced alterations of the organization of functional components essential for excitability (such as, e.g., the distribution of ion channels in the nodal and internodal regions) (Rasband and Trimmer, 2001).

Considering that the optic nerve represents an isolable central tract whose axons are exclusively myelinated by oligodendrocytes (Forrester and Peters, 1967; Sefton and Lam, 1984), we aimed our study at analyzing the ontogenic development and pharmacological sensitivity of compound action potentials (CAPs) in an in vitro optic nerve preparation of myelin mutant *taiep* rats. Our results show that, in this mutant, hypomyelination and demyelination during the first 6 months of life produce: (i) a marked reduction of the amplitude, (ii) an enhanced sensitivity to the pharmacological action of potassium channel blockers and (iii) a decreased conduction velocity of APs. We also show that these results correlate with a decompaction of myelin sheaths and with a general disorganization of the paranodal regions of the axons.

2. Results

2.1. *Abnormal postnatal development of compound action potentials in the optic nerve of taiep rats*

Supramaximal single pulse stimulation on the distal end of normal adult ONs generates CAPs at the opposite nerve end, characterized by the presence of 3 component waves, termed n_1, n_2 and n_3 (Sugioka et al., 1995), representing groups of fibers with different conduction velocities. The postnatal development of the CAPs from 10 to 180 days for control and *taiep* rats is shown in Fig. 1A. As the ON of control rats matures, the CAPs become more complex. At

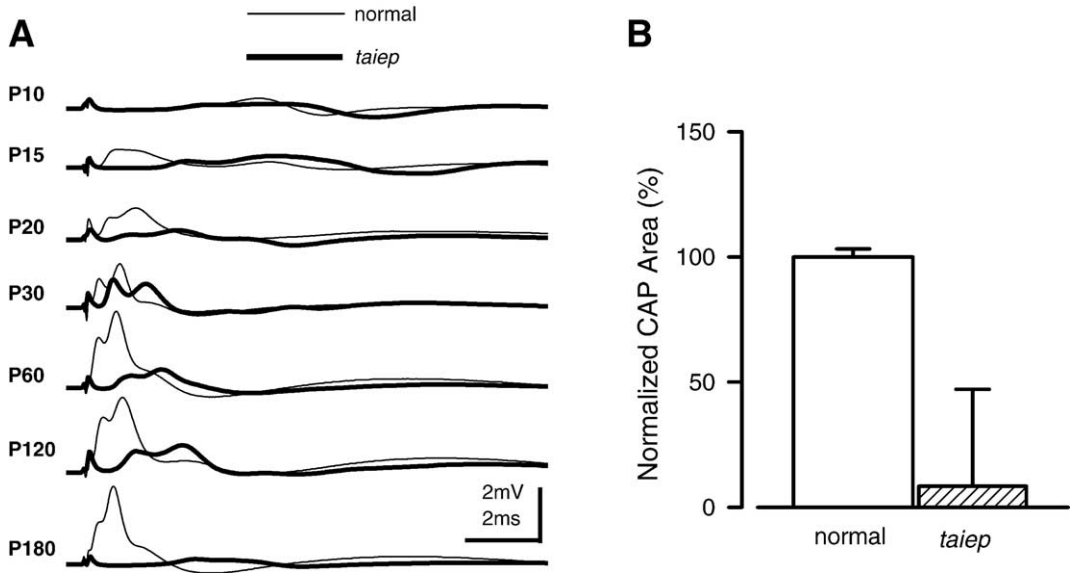

Fig. 1 – Developmental changes of optic nerve compound action potentials (CAPs) in normal and *taiep* rats. (A) Normal and *taiep* optic nerve responses to single pulses of supramaximal intensity. Each trace illustrates an average response (n = 20) at different ages (P10 to P180). All recordings presented here were obtained at constant distance from the stimulation site (3 mm). Normal maturation results in a three-wave CAP characteristic of adult optic nerve responses. After P30, all CAP components of *taiep* ONs increased their latencies and reduced their amplitudes progressively. (B) Normalized CAP areas of normal and *taiep* ONs at P60; the CAP area of *taiep* was near 10% of normal ($P < 0.001$).