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Peripheral nerve demyelination and a leptin receptor mutation: The obese Zucker rat sciatic nerve demyelination occurs with a centripetal pattern defect

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Abstract

Young male Zucker rats with a leptin receptor mutation are obese, have a non-insulin-dependent diabetes mellitus (NIDDM), and other endocrinopathies. Fine structure aspects of the tibial branches of the sciatic nerve of lean (Fa/?) and obese (fa/fa) perfused rats were compared and revealed a progressive demyelination caused by Schwann cells (SCs). There, stacked myelin layers membranes and other adhering junctions were defective in many nerve fibers of the obese rats, including of the mesaxons of the smallest fibers. Additionally, the progressive myelin alterations caused by metabolomic alterations in membrane components sorted by the SCs may also have revealed a peculiar, centripetal mode of sorting and trafficking maintenance of the peripheral nerve myelin.

Introduction

Demyelination could be acute or chronic. However, the etiology of the degenerative process related to the nourishing layer of nerve fibers, either can involve the central [CNS] [1-3] or the peripheral nervous system [PNS] [2,4-6]. It is still poorly understood, especially in the case of diabetes [7]. In textbooks, PNS neuropathies, are topics brought along with neuromuscular anomalies [8] and the defects are classified either as (a) axonal neuropathies in which insults often consist in degeneration occurring distally and secondarily to damage to the myelin or (b) as demyelinating neuropathies characterized by Schwann cell (SC) alterations in which myelin would support abnormal conduction velocities. This latter type of insidious neural defect is apparently short-sized and can appear randomly to reduce the internode myelin sheaths while maintaining the axonal content. Changes occurring in the PNS endoneurium have been seldom investigated, contrarily of what is noted for the CNS [9-11]. Recent advances also call about cooperativity between SC basal lamina components and axon revealing paracrine and juxtacrine interactions with at least one of the neuregulins [12,13].

Diabetes is known since Antiquity [7,14] but the enormous literature dealing with myelin [15] and diabetes defects is mainly clinical and metabolic, If it does share ultrastructural aspects there are many controversies in the structure and diagnostic progress of the nerve defects because human myelin samples are illustrated without pinpointing to any or how some myelin component(s) that is (are) implicated in defects [16-24]. Recently, in a murine model, similar questioning occurred [25]. More precision in this NIDDM defect about the causing flaw and mechanism would solve what becomes a huge public health concern where the Zucker rat has been introduced [26,27].

This short report complements previous data on PNS myelin fibers of the obese Zucker rat with NIDDM, where it is known the leptin receptor mutation is causing diabetes, in an equivalent way of human pathology [28]. Even though, this myelinopathy associates with co-existing endocrinopathies, it demonstrates the SC's metabolic maintenance and turnover of the myelin is important and one has tried to realize, through collection of micrographs, a sort of dynamic, sequential events of the damage throughout the myelin layers. More specifically, in continuity with a previous collection of data [29], this report further illustrates the smallest myelin anomalies of tiny nerve fibers along with other examples of adjacent large size damages found throughout some of the axon's walls. Astonishingly, our ultrastructural findings on demyelination damages could also claim that one may have also unravelled a peculiar centripetal mode of myelin maintenance by SCs in PNS nerves which can be added to another found in CNS, likely originating from nodal zone, that is longitudinal, alongside its membrane's extensions [30-32].

Materials and methods

The Institutional Animal Care and Use Committee of the Northeastern Ohio Universities College of Medicine (now Northeast

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Ohio University), Rootstown, Ohio, USA have approved the procedures of animal care, anaesthesia, euthanasia, and tissue's collection of this study and concomitant ones [29,33-35]. The collection of tissues of lean and obese Zucker young male rats have been described in detail in a recent publication, with free access [29]. These obese Zucker rats seemed to be with non-insulin dependent diabetes (NIDDM) which affliction becomes the most common and is increasing rapidly in many populations.

Results

In the previous publication, comparisons were made between light microscopy (1-µm thick epoxy sections, stained in toluidine blue) to select fields of investigations, and with those in ultrastructure of the myelin covering the nerve fibers of the sciatic tibial nerve branches [29,34]. Here, a small nerve fibre illustrated in Figure 1A of a normal rat is compared with that of an obese, i.e. diabetic one in Figure 1B. Noting the initial zone of myelin formation of the sciatic nerve branch with a SC makes an outer mesaxon with blemishes. Not only parts of the adaxonal membrane is disorganized instead of a distinct inner mesaxon structure but defects also occurred at the level of the outer mesaxon construction. Instead, a mush of membrane fragments appeared amongst a space occupied by a wrap vacuolated of waxy deposits in the diabetic nerve fibre (Figure 1B).

In the large nerve fibers of the lean rat, typical nerve myelin displayed no blemishes and a clear inner adaxonal membrane (Figure 2A) while the defects viewed in obese Zucker NIDDM rats (Figure 2B-C) not only encompassed the similar inner myelin parts but also the concentric layers of myelin membranes that showed traversed by 'funnels' initiated in the SC's Cajal zone, progressing as narrow to enlarged and intermembranous rifts of the outer to inner myelin layer, enlarging toward the adaxonal layer, thus in a centripetal diffusion pattern (Figure 2B-C). These blemishes could be caused by trans membranous defect of macromolecules involved in adherence of myelin membranes, either as extracted or missing from SC's sorting.

Discussion

Processing the obese nerve samples may either have extracted peculiar components located in the spaces between myelin layers or, more likely, these gaps filled with vacuoles and gunky sludge were already made by the NIDDM because the control and obese Zucker rat nerves were fixed a short time after perfusion fixation and processed simultaneously and in the same methodology.

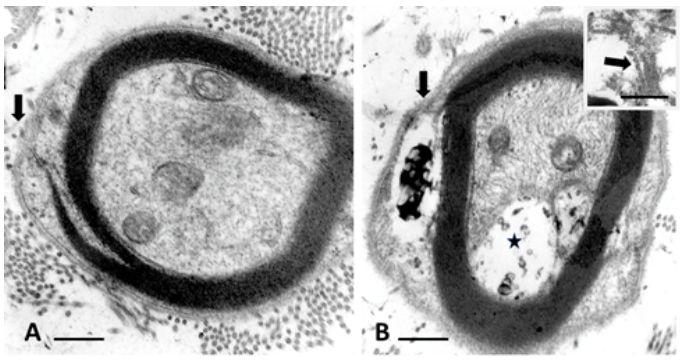

Figure 1 A-B. Small nerve fibers of lean (A) and obese (B) Zucker rat. In B: flaws in initial myelin formation of the outer mesaxon (arrows). There, the SC's Cajal band contains a space with a complex waxy deposit and the adaxonal membrane displaced develops a vacuolated space (*). Both damages accompany remains of membranes as shown in insert obtained out of another section of the same nerve fibre. Scales are 500 nm in A and b, insert ib B is 200 nm

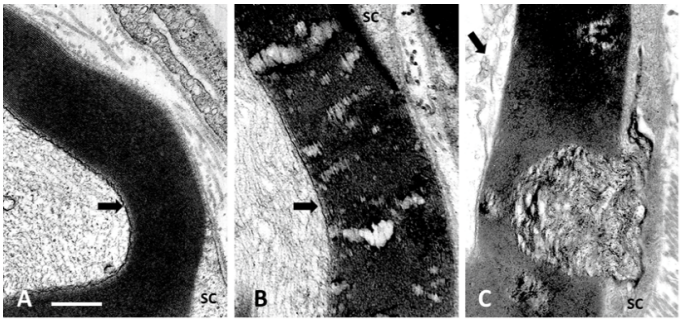

Figure 2 A-C: Parts of cross sections of large diameter myelinated nerve fibers of a lean (A) and obese (B and C) Zucker rats where the adaxonal membranes are marked by an arrow in A-C. In A: the lean rat myelin displays a regular, typical myelin wrapping. In B: channel-like damages across the myelin with C illustrating some of the complex initial wide funnel-like pockets of demyelination noted in some nerve fibers, damages appearing as wrinkled membranes initiated in the Cajal band. Scales are all equal to 500 nm

The few micrographs exemplified here are added to the defects described in previous publications and again reveal that SCs, with their continuous maintenance of the myelin, most of the burden of metabolic changes causing this defective myelin [36-41]. The SCs are imposed complex endocrine influences through which expression and sorting of some components of the myelin can be altered [29,35]. Besides the phospholipids that seemed to organize in orderly way layers, the obese Zucker peripheral nerves showed disorders similar to those of the CNS missing a plasmalogen such as the myelin basic protein in the CNS [42]. Of course, in the PNS, such as in this case, any plasmalogen (i.e. P0 or peripheral myelin protein 22), ceramide, cadherin and periaxin along with connexin 32 that contribute to the architecture and adherence of the neuroplasm, could be involved [43-51]. The altered protective insulation and nerve conduction integrity could change by wrong SC expression and sorting of membrane components in the PNS [36,41,52-60] through direct or indirect endocrine influence. In these obese rat models like in some diabetic humans, leptin plethora without receptor severs the normal hypothalamo-pituitary (and pineal?) axis functions (thyroid, growth hormone, gonadotroph and corticotroph signalling defects, circadian rhythms, etc.). There, knock out mice models would provide further information as to whether some components sorting can influence the dysmyelination associated with NIDDM peripheral nerves. Out of human diabetes autopsies and other animal diabetes data, analyses of nerves from limb amputations [61,62] where cholesterol-phospholipid balance have been altered [36,44,63-71]. Others have investigated the endoplasmic reticulum and other plasmalogens and glycolipids, especially P0 protein [72-78]. Thus, the observations support that in obese Zucker rat nerves, similarly to other animal models and, possibly the human, translates as well into congenital obesity [79-82]. Out of this non-inflammatory PNS demyelination, one can again bring the hypothesis that associated proteins and proteoglycans to the myelin [83], not only can turn over rafts [84-86] similarly as in CNS along the Schmidt-Lantermann incisures toward internode membranes [31,32] with a sort of domino effect replacement with renewed adhesive trans membrane components sorting across an already poorly zipped membranes [73]. In our case, wrong accumulations or sorting of myelin components by SCs were also viewed as flawed by insulin disruption [60] including the tiny forming mesaxons as an initial and associated disorder in the architecture alignments of the normal wrapping without being caused by osmotic processing when compared with normal nerves [29,87] and, this throughout along the changed NIDDM myelin, having components with a centripetal insertion, viewed by the evidenced growing blemishes making sorts of trans membranous

passageways across the sort of liquid crystal-like phase between myelin strata could be created by a sort of Rayleigh-Taylor instability [88,89]. In this case, at first, accumulated molecular species passing throughs, appear by accumulations as a processing channel-like, with centripetal orientation, widen into sectors caused by the progressively changed myelin composition.

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