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Effects of early and late diabetic neuropathy on sciatic nerve block duration and neurotoxicity in Zucker diabetic fatty rats

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Editor's key points

- Most studies of diabetic neuropathy use rat models of type I diabetes.
- This study used a more relevant model of type II diabetes.
- Sciatic nerve bock duration and neurotoxicity were studied.
- Motor block was prolonged in rats with neuropathy, but there was no evidence of nerve injury.

Background. The neuropathy of type II diabetes mellitus (DM) is increasing in prevalence worldwide. We aimed to test the hypothesis that in a rodent model of type II DM, neuropathy would lead to increased neurotoxicity and block duration after lidocaine-induced sciatic nerve block when compared with control animals.

Methods. Experiments were carried out in Zucker diabetic fatty rats aged 10 weeks (early diabetic) or 18 weeks (late diabetic, with or without insulin 3 units per day), and age-matched healthy controls. Left sciatic nerve block was performed using 0.2 ml lidocaine 2%. Nerve conduction velocity (NCV) and F-wave latency were used to quantify nerve function before, and 1 week after nerve block, after which sciatic nerves were used for neurohistopathology.

Results. Early diabetic animals did not show increased signs of nerve dysfunction after nerve block. In late diabetic animals without insulin *vs* control animals, NCV was 34.8 (5.0) *vs* 41.1 (4.1) ms s^{-1} ($P<0.01$), and F-wave latency was 7.7 (0.5) *vs* 7.0 (0.2) ms ($P<0.01$), respectively. Motor nerve block duration was prolonged in late diabetic animals, but neurotoxicity was not. Late diabetic animals receiving insulin showed intermediate results.

Conclusions. In a rodent type II DM model, nerves have increased sensitivity for short-acting local anaesthetics without adjuvants *in vivo*, as evidenced by prolonged block duration. This sensitivity appears to increase with the progression of neuropathy. Our results do not support the hypothesis that neuropathy due to type II DM increases the risk of nerve injury after nerve block.

Keywords: local anaesthetics; nerve block; neuropathy, diabetic; neurotoxicity

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Diabetic peripheral neuropathy (DPN) is a frequent complication of both type I and type II diabetes mellitus (DM), and the most prevalent neuropathy in the Western world.[1] Diabetics undergo surgery more often than non-diabetic patients,[2] and several surgical procedures for typical complications of long-standing DM, for example, creation of arteriovenous fistula in patients with end-stage renal disease, might be preferably performed under regional anaesthesia.[3]

However, diabetic neuropathic nerves may be more sensitive to local anaesthetics and their toxicity, and this hypothesis is supported by two lines of evidence. First, regional anaesthesia in diabetic neuropathic patients may be associated with increased risk of neurological injury.[4] Limited epidemiological evidence suggests higher risk of neurotoxicity in diabetic neuropathic patients,[5 6] even if experimental evidence has been equivocal.[7] Secondly, DPN may influence nerve block duration.[4] Clinical[8 9] and experimental[10 11] evidence suggests that block duration may be prolonged in diabetic neuropathic nerves. However, most studies were carried out in models of streptozotocin-induced type I DM, which does not reflect clinical reality, in which the huge majority of patients suffer from type II DM.[5 7]

Our aim was to determine the impact of regional anaesthesia in DPN in an animal model for type II DM. We therefore sought to devise a comprehensive model using behavioural, electrophysiological, and histopathological investigations to determine neurotoxicity of a lidocaine 2% peripheral nerve block and duration of this nerve block in Zucker diabetic fatty

(ZDF) rats with early and advanced diabetic neuropathy, with and without partial glycaemic control. Our working hypothesis was that in a rodent model of type II DM, the presence of advanced (18 weeks) but not early (10 weeks) neuropathy would lead to increased neurotoxicity and block duration after sciatic nerve block with lidocaine when compared with age-matched healthy control animals. The primary endpoint was neurohistopathology 1 week after nerve block.

Methods

The study protocol was approved by the Institutional Animal Care and Use Committee of the Academic Medical Center, University of Amsterdam, protocol number LEICA102868-1. Methods and results are reported according to relevant ARRIVE guidelines.[12]

Animals

Experiments were undertaken in ZDF rats, which were obtained from Charles River Laboratories (L'Arbresle, France). This inbred model of type II DM combines a genetic predisposition (homozygous leptin receptor mutation fa/fa, 'diabetic', or heterozygous mutation fa/+, 'control') with a dietetic component (Purina #5008 diet, Charles River, L'Arbresle, France).[11 13] Animals were obtained at 9 weeks of age and were allowed to acclimatize for 1 week. For all electrophysiological measurements, sciatic nerve block, and placement of insulin release implants, animals were anaesthetized using isoflurane (Baxter, Utrecht, The Netherlands) with an inspiratory concentration between 2 and 3 vol%, since this regimen least affects electrophysiological measurements in rodent models.[14] Adequacy of anaesthesia was ascertained by lack of a pedal withdrawal response to a nociceptive stimulus. All procedures were performed percutaneously, and the analgesic rescue protocol was buprenorphine (0.05 mg kg^{-1} body weight). Detailed welfare assessment was undertaken by an animal care technician unrelated to the experiment. After the last measurements, while still under isoflurane anaesthesia, animals were killed using CO_2 narcosis.

Experimental groups

The timeline of experimental procedures is given in Figure 1. In all experimental groups, baseline measurements of electrophysiological parameters (see below) were taken at 10 weeks of age.

Group 'early control (EC)' were 6 ZDF fa/+ animals, and group 'early diabetic (ED)' were 10 ZDF fa/fa animals undergoing left sciatic nerve block immediately after baseline testing at 10 weeks. One week later, behavioural and electrophysiological measurements were repeated, and the left sciatic nerve was excised for neurohistopathological evaluation.

The group 'late control (LC)' consisted of 10 fa/+ animals kept until 18 weeks of age. The group of diabetic animals for

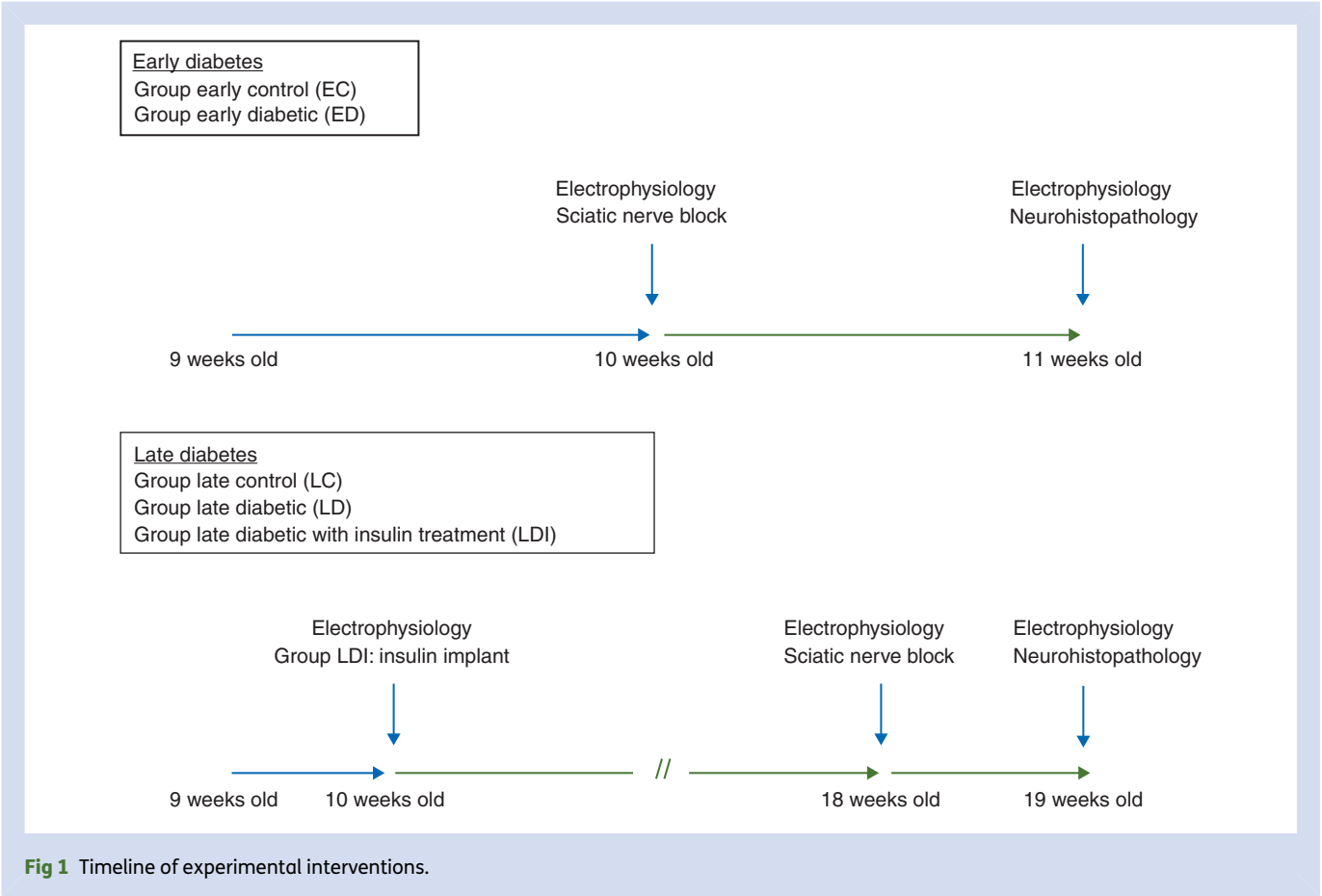

Fig 1 Timeline of experimental interventions.