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Effects of insulin on peripheral nerves

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ABSTRACT

Aims: To assess the effects of insulin on peripheral nerve under normoglycemic and hyperglycemic conditions in the presence and absence of anoxia.

Methods: This study uses the in-vitro sciatic nerve model to assess the effect of insulin on peripheral nerve with the nerve action potential (NAP) as an index of nerve function.

Results: Under normoglycemic conditions, low concentrations of regular insulin (0.01 nM) reduced the conduction velocity of oxygenated nerves. Hyperglycemia increased the duration of the NAP and this increase was nearly completely eliminated by insulin in the 0.1 nM–100 nM concentration range. Insulin (1 nM) also had effects on normoglycemic nerves exposed to intermittent anoxia, producing a decrease in the paired-pulse response and NAP amplitude and an increase in peak duration. This was associated with a reduced time to anoxia-induced conduction block. Similar effects were seen when regular insulin was replaced by insulin detemir, but the latter required much higher concentrations.

Conclusions: Insulin has concentration dependent effects on the peripheral nerve that are dependent on glucose and anoxia. These effects may be important in modulating neuropathic consequences of diabetes.

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1. Introduction

Neuropathy is a serious complication which occurs in roughly half of diabetic patients (Abbott, Malik, van Ross, Kulkarni, & Boulton, 2011; Karvestedt et al., 2011). Although there are many therapies directed at mitigating the pain associated with diabetic neuropathy, disease modifying therapies have had limited efficacy, especially in type 2 diabetes (Callaghan, Little, Feldman, & Hughes, 2012). This is the impetus to investigate the importance of various processes that could contribute to diabetic neuropathy. One field of active investigation focuses on insulin signaling in the peripheral nerve (Grote, Ryals, & Wright, 2013; Grote et al., 2013). While insulin has numerous effects on cells (Wilcox, 2005), relatively little is known about the specific effects of insulin on peripheral nerve (Kim & Feldman, 2012). Unlike adipocytes and muscle, glucose uptake in Schwann cells or axons is not insulin dependent (Muona, Sollberg, Peltonen, & Uitto, 1992; Tomlinson & Gardiner, 2008). Glucose uptake in Schwann cells is dependent on the glucose transporters GLUT1 and GLUT3 which are not insulin dependent (Magnani et al., 1996). Glucose uptake in the peripheral nerve axons is dependent mainly on GLUT3 and the primary glucose transporter in the blood–nerve barrier which regulates the glucose concentration in the periaxonal milleau (Kanda, 2013; Weerasuriya & Mizisin, 2011) is GLUT1 (Takata, Hirano, & Kasahara, 1997; Tserentsoodol, Shin, Koyama, Suzuki, & Takata, 1999).

On the other hand, insulin does modify the utilization of glucose through the control of the phosphorylation of a large number of enzymes (Yugi et al., 2014) which regulate glycogen concentration, glycolysis and gluconeogenesis. Insulin binding to the insulin receptor stimulates phosphorylation of the insulin receptor substrates (IRS) which modify the action of phosphatidylinositol-3kinase (PI3-K) in phosphorylating Akt (Kim & Feldman, 2012) and inactivating glycogen synthase kinase-3β (GSK-3β) and protein kinase A (PKA) (Brady & Saltiel, 2001). This enhances the activity of glycogen synthase and the production of glycogen. Protein phosphatase 1 (PP1) is activated by insulin, which in turn inhibits glycogen phosphorylase and phosphorylase kinase (Brady & Saltiel, 2001) and suppresses glycogen breakdown. Insulin also stimulates glycolysis by dephosphorylating pyruvate kinase (PK) and 2,6-biphosphate kinase, which control important reactions in the glycolysis. The production of acetyl-CoA and the flux through gluconeogenesis are dependent on pyruvate dehydrogenase that is also regulated by insulin (Wilcox, 2005).

A direct effect of insulin on the peripheral nerve may contribute to the acute painful neuropathy that can occur with the initiation of insulin treatment for diabetes called “insulin neuritis” or treatment onset neuropathy (Gibbons & Freeman, 2015; Knopp, Srikantha, & Rajabally, 2013; Llewelyn, Thomas, Fonseca, King, & Dandona, 1986). However, neuropathic symptoms may occur with aggressive glucose lowering therapies that do not involve insulin (Gibbons & Freeman,

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2010) and so a direct effect of insulin is difficult to confirm. A similar issue applies to many clinical studies such as the Diabetes Control and Complications Trial (DCCT) (Anonymous, 1995) and ACCORD (Calles-Escandon et al., 2010; Pop-Busui et al., 2010; Vinik, Maser, & Ziegler, 2010) studies since it is difficult to separate effects of insulin from the secondary effects of hypoglycemia. One clinical study that may have relevance was performed by Kwai et al. (2014) who found that a continuous insulin infusion improves axonal function while patients receiving multiple doses of insulin during the day producing peaks and troughs in both insulin and glucose levels demonstrated neurophysiologic markers of nerve injury. This might suggest that there could be injury due the high peak concentrations following the insulin bolus.

In order to enhance our knowledge of insulin's effects on whole nerves, this paper will study how insulin changes the peripheral nerve NAP (nerve action potential) in-vitro system, where the effects of insulin can be separated from those of glucose and anoxia.

2. Methods

2.1. Experimental setup

A more detailed description of the methods is given in previous papers (Baylor & Stecker, 2009; Stecker & Baylor, 2009; Stecker & Stevenson, 2013, 2015). Under a protocol approved by the IACUC (Winthrop University Hospital Protocol, WUH-MS#1), a total of 148 nerves from 74 Sprague–Dawley rats (Hilltop, Scottdale, PA) were studied. The rats were male retired breeders with an average age of 32 weeks (range of 25–48 weeks). Each sciatic nerve was dissected and placed into a perfusion chamber and stimulated using stainless steel sub-dermal electrodes arranged in a tripolar array (Fig. 1). The stimulus consisted of paired unipolar pulses separated by 4 ms, each with a 15 mA peak current, a duration of 0.01 ms and an overall pair repetition rate of 5 Hz. Recordings were made from paired recording electrodes on an average of 1 cm away from the stimulating electrodes. Recorded signals were digitized at 99 kHz/channel, averaged and stored every 4 s.

Each experiment lasted at least 16 h and could be classified into two main groups: continuously oxygenated or intermittent anoxia, as outlined in Fig. 1. In the intermittent anoxia experiments, the nerve was initially exposed to oxygenated perfusate but then, after 60 min, the nerve was subjected to 90 min periods of oxygenation followed by 90 min of anoxia. A simplified description of the time course of changes in the NAP is reflected in the average of each NAP parameter during the third, fifth, seventh, ninth and eleventh 90 min time period during the experiment (Fig. 1). These time points are termed T1, T2, T3, T4 and T5 respectively (Fig. 1). In the intermittent anoxia experiments, each of these time periods corresponded to the period of oxygenation immediately following a period of anoxia.

All experiments were performed with the nerve maintained at 36 °C. The base perfusate was composed of 10 mM HEPES, 110.2 mM NaCl, 17.8 mM $NaHCO_3$, 4.0 mM MgSO4, 3.9 mM KCl, 3.0 mM KH_2PO_4 1.2 mM $CaCl_2$. The perfusate also contained D-glucose at either 5.5 mM (which would be a normal serum glucose for a non-diabetic rat) or 55 mM. Nerves were exposed to insulin (Novolin-R) concentrations of 0, 0.01 nM, 0.1 nM, 1 nM, 10 nM, 100 nM and 1000 nM. These concentrations bracket the normal range of blood insulin concentrations of approximately 0.076–.11 nM in the fasting

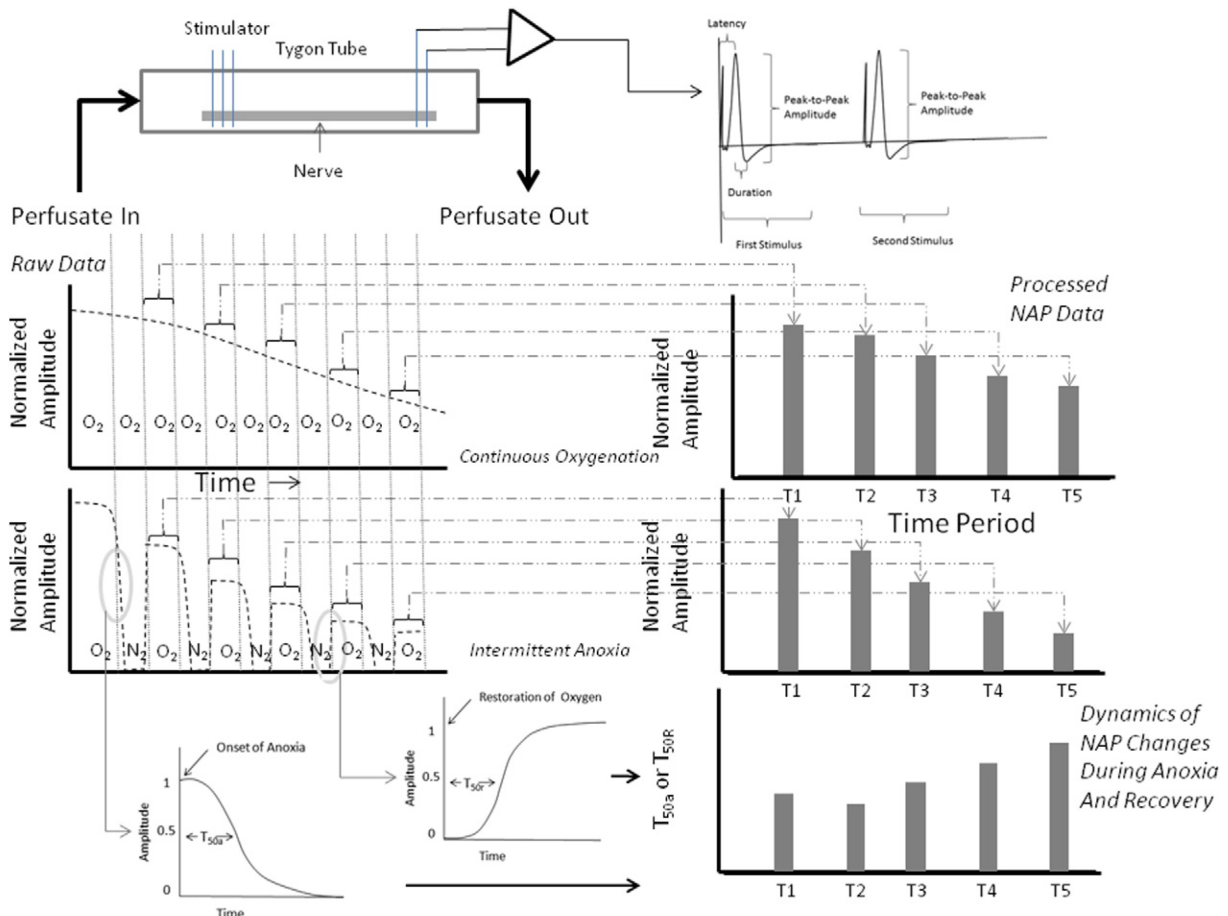

Fig. 1. Illustration of the experiment giving outline of the raw data and how data are abstracted for analysis.

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