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# Global Diabetes 2016: A correlative relationship between chronic pain and insulin resistance in Zucker fatty rats: role of down regulation of insulin receptors - Shuxing Wang - Xinxiang Medical College

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**Abstract**

Epidemiological studies and meta-analyses report a strong relationship between chronic pain and abnormalities in glucose metabolism, but the exact relationship between chronic pain and insulin resistance in type-2-diabetes (T2D) remains unknown. Using a model of neuropathic thermal and tactile hypersensitivity induced by chronic constriction sciatic nerve injury (CCI) in Zucker diabetic fatty (ZDF) and Zucker lean (ZL) littermates, we compared the recovery period of hypersensitivity and therefore the progression of T2D and studied the possible involvement of insulin receptors (IR) within the comorbidity of those two conditions. We found that the nociceptive thresholds to thermal and mechanical stimulation in naïve ZDF rats were lower than in ZL littermates at 6 weeks of age. Although both ZDF and ZL rats developed thermal and tactile hypersensitivity after CCI, it took an extended time for the nociceptive sensitivity to revive in ZDF rats. Meanwhile, nerve injury accelerated the progression of T2D in ZDF rats, demonstrated by an earlier onset of hyperglycemia, more severe hyperinsulinemia, and a better concentration of glycosylated hemoglobin (HbAlc) six weeks after CCI, as compared to those in naïve ZDF and ZL rats. IR-immunoreactivity cells were located across the central nervous system 40; CNS41; and skeletal muscles. In the CNS, IR co-expressed with a neuronal marker (NeuN) but not a glial marker (GFAP).

**Perspective:**

Nerve injuries in genetically susceptible individuals may accelerate the development of insulin resistance as in type 2 diabetes. A downregulated expression of insulin receptor in the skeletal muscle innervated by the injured nerve is one of the underlining mechanisms.

**Keywords:** Chronic hypersensitivity, insulin resistance, type 2 diabetes, CCI, HbAlc, insulin receptor, Zucker diabetic fatty rats.

**Introduction:** Type-2-diabetes (T2D) is a complex metabolic disorder characterized by hyperglycemia and hyperinsulinemia. The incidence of obesity, insulin resistance, and T2D is increasing at an alarming rate and represents a big clinical condition worldwide. T2D is frequently accompanied with painful diabetic neuropathy, among many other complications. Approximately one in three people with diabetes is suffering from diabetic neuropathy, a serious ill health which will present with excruciating pain and is liable for substantial morbidity, increased mortality, and impaired quality of life. However, the precise relationship between chronic pain and T2D remains unclear. The genetically leptin-receptor deficient ZDF rats develop obesity, insulin resistance, and T2D naturally. In this study, we used ZDF rats as a diabetic model and ZL rats as control to study a correlative relationship between the progression of T2D and changes in nociceptive threshold. We also examined whether there is a down regulated expression of insulin receptors in the central nervous system in this process.

**Methods:**

**1. Diabetic animal model:** Zucker diabetic fatty (fa/fa) (ZDF, n=35) rats and Zucker lean (+/fa) (ZL, n=21) littermates five weeks old were purchased from Vital River Laboratories International Inc. (Beijing, China). The number of rats was calculated using power analysis (0.8), considering the data variation of post operation nociceptive behavior and of blood glucose level in ZDF rats. Littermates from the same or foster mother were housed in a specific pathogen free condition, in a large plastic cage with wood chip bedding, distilled water, and standard rat diet pellets available ad libitum. Animals were housed under controlled temperature (21°C±2°C), relative humidity (50%±10%) and artificial light (12 h light/dark cycle, lights on at 7 A.M.). Rats entered the experimental procedures (divided into three separate experiments, A, B, and C) at six weeks of age, as illustrated in figure 1A, 1B, and 1C.

**2. Preparation of CCI or Sham Animals**: In this study chronic constriction injury of a unilateral sciatic nerve (CCI) was produced by placing loose ligations at the common sciatic nerve according to the method of Bennett and Xie. Briefly, fewer than 2% isoflurane anesthesia, the right side sciatic nerve was exposed in the mid-thigh and four loose ligatures with 1.0-1.5 mm intervals were made around the nerve trunk using 4-0 chromic gut suture. The nerve trunk was then put back its original position and the wound closed using sterilized wound clips. Sham rats were made following the same surgical procedure except for the nerve ligation. No further analgesics were used following the CCI or sham operation to avoid any unwanted affection.

**3. Behavioral Testing**: The experiment A was meant to compare the nociceptive threshold at baseline and following operation between CCI operated ZDF (n=7) and ZL (n=5) rats without considering sham operation with the purpose of saving rats. A ZDF rat was excluded from further experiments due to posGlucose concentration testing. In experiment B, rats (ZDF, n=18; ZL, n=10) were tested for random glucose concentration using Ascensia Breeze Blood Glucose Monitoring System (Newbury, Berks, UK). The glucose concentration is used as a routine test to determine the progression of blood glucose metabolism dysfunction.

**4. Glucose Concentration Testing**: In experiment B, rats (ZDF, n=18; ZL, n=10) were tested for random glucose concentration using Ascensia Breeze Blood Glucose Monitoring System (Newbury, Berks, UK).

**5. Plasma Glycohemoglobin Concentration**: Hemoglobin A1c (HbA1c) is a minor hemoglobin component of erythrocytes and its sugar moiety is glucose covalently bound to the terminal amino acid of the beta chain.

**Discussion:** In this study we found that 1) ZDF rats have a lower nociceptive threshold, 2) ZDF rats with CCI showed a delayed restoration from nociceptive hypersensitivity, and 3) the presence of nociception in ZDF rats accelerated the progression.

**Results:** Lower nociceptive threshold and prolonged recovery period of nociceptive sensitivity in ZDF rat; Deteriorated glucose metabolism in ZDF rats with CCI; Correlation between nociceptive threshold and glucose concentration in ZDF rats.

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