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# Effects of diabetic neuropathy on cardiovascular response to noxious stimuli in streptozotocin-induced diabetic rats

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## Introduction

Diabetes can be associated with a number of peripheral neuropathies [1,2,3] . Patients with diabetes may have altered cardiovascular responses to noxious stimuli,although the details remain unclear.

## Materials and Method

Experiments were performed on 14 male Sprague Dawley rats (aged 8 weeks) weighing between 250-270 g.

- Diabetes model (DM) rats were prepared by administering streptozotocin (STZ; 60 mg/kg, i.p.).
- Three weeks after STZ treatment, a radio transmitter with a pressure sensor and electrodes leads were implanted to measure the blood pressure (BP) and heart rate (HR) (Fig. 1).
- Four weeks after STZ treatment, a formalin test was conducted on the left upper lip. Pain-related behavior (PRB), BP, and HR were recorded for 60 min.
- Two hours after the formalin injection, rats were sacrificed to evaluate the expression of c-Fos in the caudal part of the spinal trigeminal nucleus (Vc).
- Furthermore, BP and HR variability were analyzed by the Memcalc method. Baroreceptor sensitivity (BRS) was measured by the spontaneous sequence method[4].
- Results are expressed as the mean ± SD. Statistical analyses were performed using an unpaired t-test for comparisons of baseline values between two groups. ANOVA for two-way repeated measures followed by Dunnett's test were used for comparisons of group differences. A $p$ value < 0.05 was considered significant.

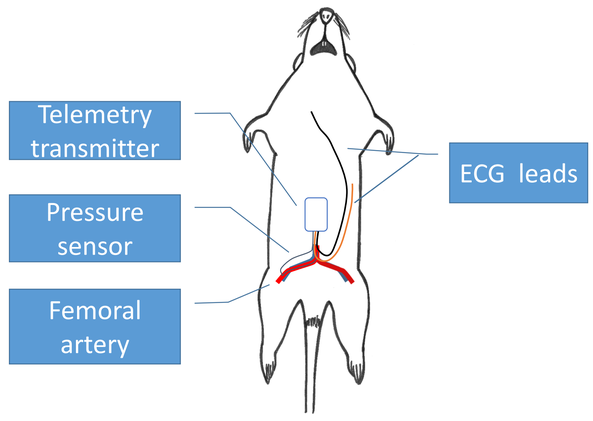


Fig. 1 Placement of the telemetry transmitter with electrode leads and pressure sensor

## Result

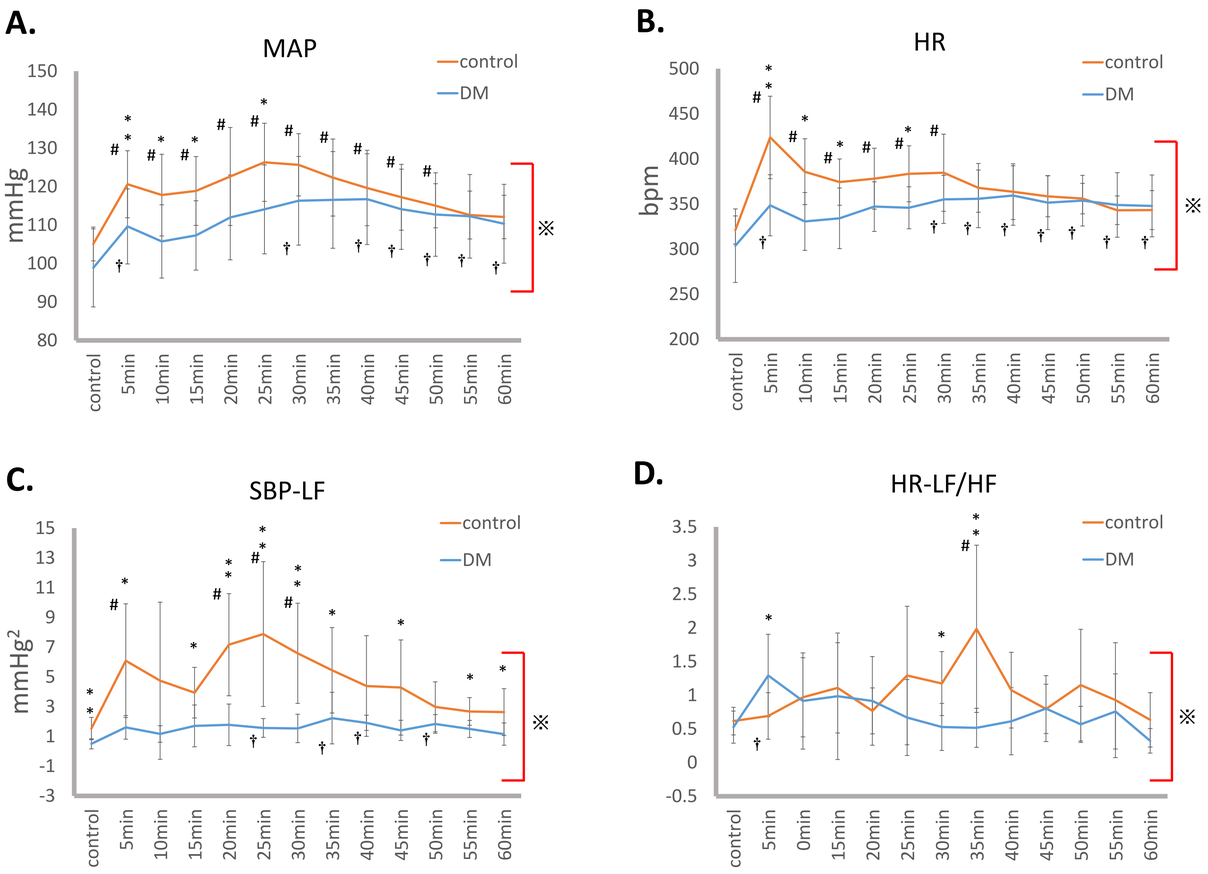


Fig. 2 The time course of mean arterial pressure (**A**; MAP), Heart rate (**B**; HR), the low frequency band of systolic BP variability (**C**; SBP-LF) and the ratio of the low frequency band and high frequency band of HR variability (**D**; HR-LF/HR). The elevation in MAP and HR in DM rats was smaller than that in control rats ($p$ < 0.01). Changes in SBP-LF and HR-LF/HF in DM rats were significantly less compared with those in control rats ($p$ < 0.01). * significant difference between DM rats and control rats (*, $p$ < 0.05; **, $p$ < 0.01). # significant difference between control and each time point in control rats ($p$ < 0.05). † significant difference between control and each time point in DM rats ($p$ < 0.05). ※ significant interaction between control and DM rats ($p$ < 0.05).

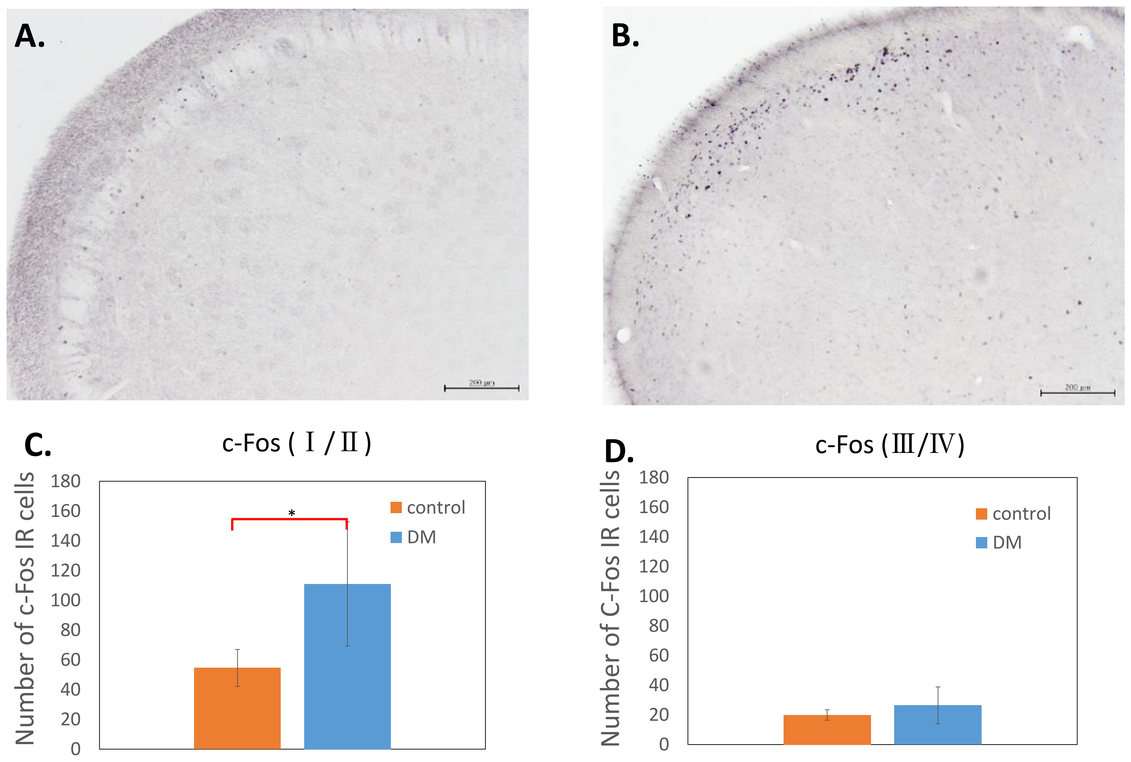


Fig 3. Expression of c-Fos immunoreactive cells in the caudal part of the spinal trigeminal nucleus (Vc). **A.** Photomicrograph showing c-Fos immunoreactive cells in the ipsilateral Vc at 1850 μm caudal to the ovex at 100× magnification in control rats.
**B.** Photomicrograph showing the same position as A in DM rats. **C,D.** The mean number of c-Fos IR cells in segments from the ovex to 2460 μm caudal to the ovex is shown. The expression of c-Fos in lamina Ⅰ and Ⅱ of the Vc was higher in DM rats than that in control rats ($p$ < 0.05). However, there was no significant difference between lamina Ⅲ and Ⅳ of the Vc.

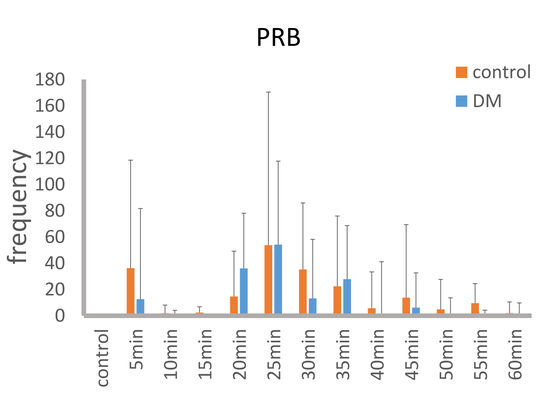


Fig. 4 Time course of pain-related behavior (face rubbing, PRB) after injection of 50 μl of 4% formalin into the left upper lip. There was no significant difference between control and DM rats.

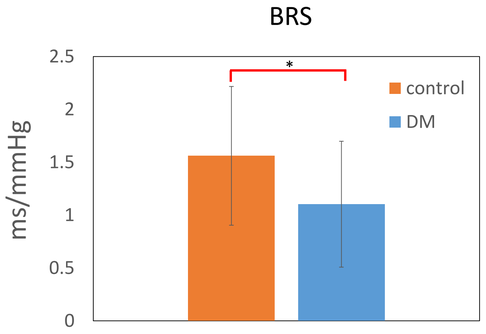


Fig.5 Baroreflex sensitivity determined by the spontaneous sequence method.
* significant difference between DM rats and control rats ($p$ < 0.05).

## Discussion

Expression of c-FOS in the Vc in response to noxious stimuli was significantly higher in DM rats than in control rats, suggesting enhanced pain perception in the first relay nucleus in the trigeminal sensory system. However, the hemodynamic and autonomic response to the noxious stimuli was lower in DM rats than in control rats. These results suggest that both the sensory and cardiovascular autonomic nervous system is modulated by central and peripheral diabetic neuropathy.

## References

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4) Geza G, *et al*: Baroreceptor reflex is suppressed in rats that develop hyperalgesia behavior after nerve injury; Pain 2009, 146(3):293-300.