Perivascular sympathetic neuropathy in the streptozotocin type I diabetic rat model

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Impaired neural control of arteries is implicated in the etiology of diabetes related complications such as diabetic foot. While there is evidence that diabetes impairs neurovascular transmission in animals, there are no reports that sympathetic axons are lost. Here we investigated the effects of streptozotocin (STZ)-induced type I diabetes on rat plantar metatarsal arteries (PMAs). Rats treated with STZ (60 mg/kg, i.p.) received 1 unit/day (n = 6) or 4 units/day (n = 7) of insulin. Rats treated with a low-dose of insulin had elevated blood glucose levels (>20 mM) whereas those treated with a high-dose maintained blood glucose levels <15 mM. After 12 weeks, PMAs were dissected from rats that had been deeply anaesthetized with isoflurane and killed by exsanguination. Segments of PMAs were mounted in myographs and their responses to electrical stimulation and α-adrenoceptor agonists were assessed. The remaining tissue was fixed and immuno-labeled with anti-tyrosine hydroxylase (TH) and anti-synaptophysin. The axon plexus was imaged and quantified in terms of the number, TH+ brightness and length of the fluorescent structures intercepting horizontal lines placed on the image. The nerve- and agonist-evoked responses of arteries from rats receiving either dose of insulin did not differ from control. There was also no difference in the % area covered by nerve plexus between control and diabetic groups. However, PMAs from diabetic rats receiving a low dose of insulin had a reduced frequency, but an increased TH+ brightness and length, of fluorescent intercepts ($P < 0.05$). These measures were unchanged in the high-dose insulin group. Therefore, despite failure to detect a change in neurovascular transmission, there were changes in the sympathetic innervation of PMAs from diabetic rats. These changes were not observed in diabetic rats receiving a high dose of insulin and most likely result from hyperglycemia. This makes PMAs a suitable model to assess the development and prevention of diabetes-induced sympathetic neuropathy.