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Supersensitivity to both tyramine and noradrenaline in diabetic autonomic neuropathy

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SUMMARY Cardiovascular responses to intravenously infused tyramine and noradrenaline were measured in five normal subjects, five insulin-dependent diabetics and five insulin-dependent diabetics with autonomic neuropathy. Tyramine infusion produced a statistically significant increase in systolic blood pressure (BP) in the autonomic neuropaths only ($p < 0.001$). No change occurred in diastolic BP. Noradrenaline infusion produced a statistically significant increase in systolic BP in the normal subjects ($p < 0.01$) and in the autonomic neuropaths ($p < 0.001$). The increase in systolic BP in the neuropaths was significantly greater ($p < 0.001$) than in normal subjects. Diastolic BP rose significantly only in the normal subjects ($p < 0.05$). There was no change in heart rate in response to either agent. Thus super-sensitivity to noradrenaline occurred in patients with diabetic autonomic neuropathy indicating post-denervation hypersensitivity. Tyramine hypersensitivity also occurred indicating that denervation is not complete and suggesting dysfunction at a pre-synaptic level.

Disorders of the autonomic nervous system are increasingly recognised in diabetic patients. Abnormal cardiovascular reflexes are frequently found, even in the early stages of autonomic neuropathy, and, indeed, their presence is often used as a diagnostic test. However, the functional or anatomical site of the lesion involved in autonomic neuropathy has not been identified. The use of pressor drugs has been put forward as a means of assessing the site of the lesion on the autonomic reflex arc in conditions associated with chronic autonomic failure[1] such as the Shy-Drager syndrome but has not been performed in diabetic autonomic neuropathy. The aim of the present study was to attempt to identify the site of the lesion in diabetic autonomic neuropathy by means of examining the cardiovascular responses to intravenously infused tyramine (an indirectly-acting sympathomimetic) and noradrenaline.

Subjects and methods

Three groups of subjects were studied. Group I comprised five normal subjects (four male, one female) with a mean age of 49 years (range 44–56 years); none had evidence of neuropathy. Group II included five insulin-dependent diabetic patients (four male, one female) with a mean age of 46 years (range 24 to 56 years) and mean duration of diabetes of 13 years (range 10 to 20 years). All had been carefully studied and shown to have no evidence of autonomic neuropathy as defined as loss of beat-to-beat variation in heart rate and an abnormal heart rate response to the Valsalva manoeuvre. Group III comprised five insulin-dependent diabetic patients (four male, one female), mean age 48 years (range 38 to 67 years) and mean duration of diabetes of 20 years (range 6 to 31 years). These patients were studied as above and showed definite evidence of autonomic neuropathy.

No subject had a history of cardiac disease, all had a normal electrocardiogram and no medications, other than insulin, were taken.

Ethical permission for the study was obtained from the hospital ethical committee and written consent was obtained from the participants after detailed explanation of the study.

The diabetic patients were admitted to hospital at 1800 hours on the evening prior to the study. Where relevant, the normal dose of evening insulin was omitted. A continuous intravenous infusion of Actrapid insulin was instituted shortly after admission and the infusion rate adjusted to maintain the blood glucose between 4 and 6 mmol/l throughout the period of the study. All subjects were fasted from midnight and were kept supine throughout. They were allowed to drink water ad lib. Indwelling venous cannulae were inserted into right and left antecubital veins, one being

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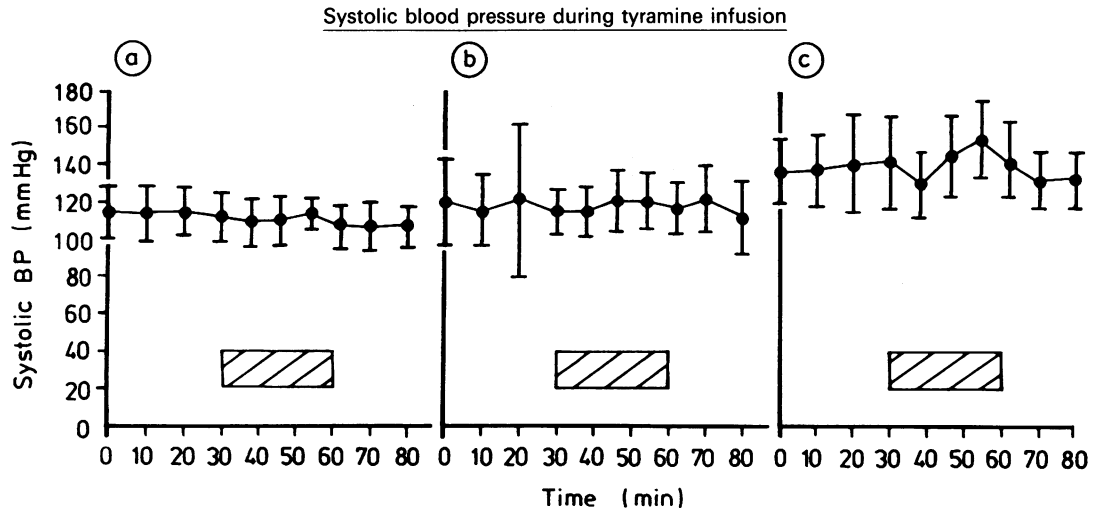

Fig 1 *The effect of an intravenous infusion of tyramine on systolic blood pressure (mean ± SD) in five normal subjects (A), five diabetic patients without neuropathy (B) and five diabetic patients with autonomic neuropathy (C).*

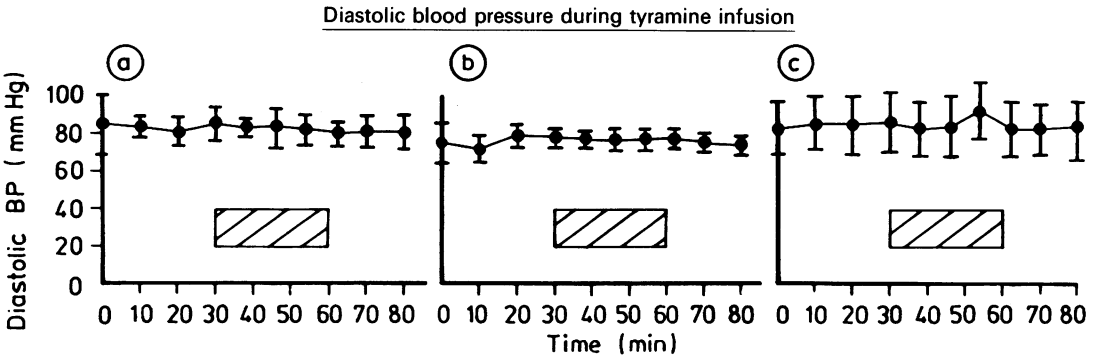

Fig 2 *The effect of an intravenous infusion of tyramine on diastolic blood pressure (mean ± SD) in five normal subjects (A), five diabetic patients without neuropathy (B) and five diabetic patients with autonomic neuropathy (C).*

used for infusions and the other for sampling.

After a 30 minute control period tyramine was infused intravenously in a stepwise manner. The initial infusion rate was 1 μg/kg/min. Each infusion period lasted 4 min and the rate was increased each time by 1 μg/kg/min up to 7 μg/kg/min. Following the last tyramine period, no infusions were performed for one hour when noradrenaline was infused at 0·01 μg/kg/min for 20 minutes, 0·02 μg/kg/min for another 20 minutes and 0·04 μg/kg/min for a further 20 minutes.

Radial pulse rate and supine blood pressure were measured at 5 minute intervals during control and recovery periods and at 2 minute intervals during infusion periods. Blood pressure was measured with an automatic blood pressure recorder with an external cuff (Arterosonde 1217 Roche).

Statistical methods

The periods of infusion of sympathomimetic agents were examined by fitting regression lines to the data points. Analysis of variance was then performed on each group to assess whether the regression line for the group differed significantly from horizontal representing a positive (or negative) pressor response. Differences between groups were assessed for significance by analysis of variance.

Results

Tyramine infusion No change in systolic blood pressure occurred in Group (I) [normal controls] or Group (II) [diabetic patients with no demonstrable neuropathy] (fig 1A and B) but mean systolic BP rose significantly from

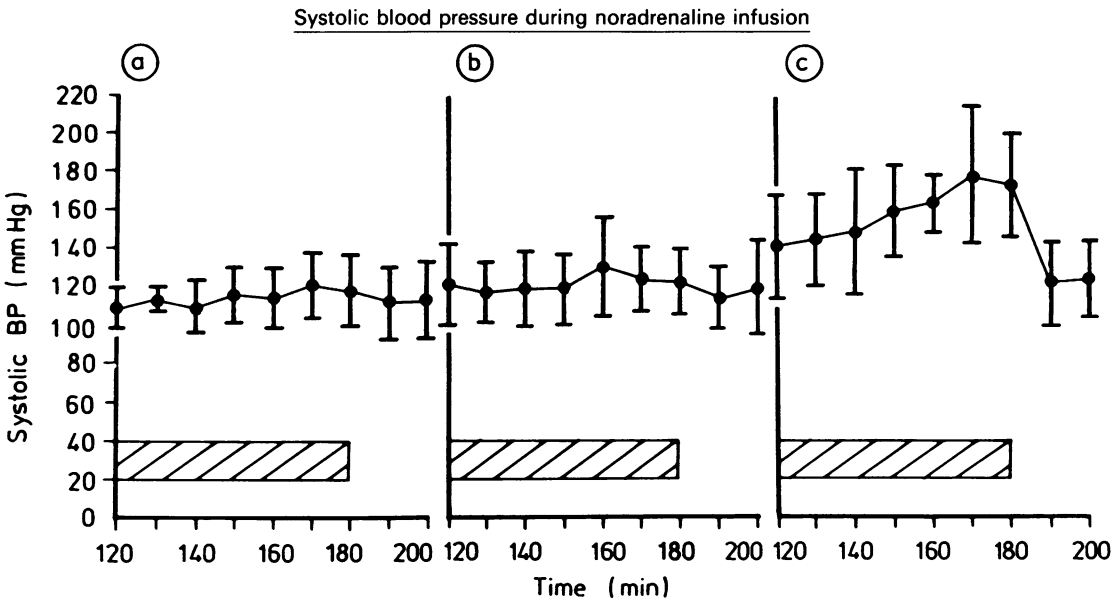

Fig 3 *The effect of an intravenous infusion of noradrenaline on systolic blood pressure (mean ± SD) in five normal subjects (A), five diabetic patients without neuropathy (B) and five diabetic patients with autonomic neuropathy (C).*

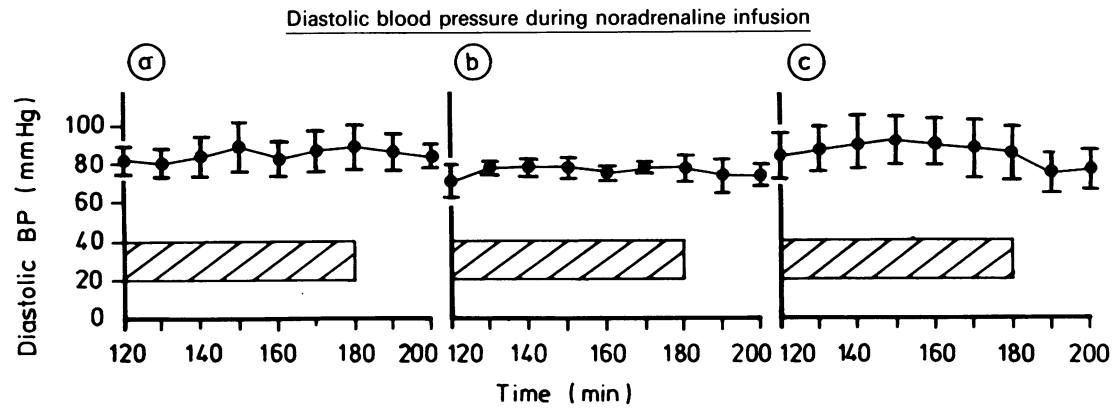

Fig 4 *The effect of an intravenous infusion of noradrenaline on diastolic blood pressure (mean ± SD) in five normal subjects (A), five diabetic patients without neuropathy (B) and five diabetic patients with autonomic neuropathy (C).*

142 mm Hg ± 23 to 151 mm Hg ± 13 [$p < 0.001$] in Group (III) [diabetic patients with autonomic neuropathy] (fig 1C). There was no significant change in diastolic BP in any group (fig 2), nor in heart rate.

Noradrenaline infusion Mean systolic BP increased significantly in Group (I) from 109 mm Hg ± 9 to 118 mm Hg ± 19 [$p < 0.01$] and in Group (III) from 141 mm Hg ± 24 to 173 mm Hg ± 25 [$p < 0.001$] (fig 3A and C). The rise in mean systolic BP was however significantly greater in Group (III) than in Group (I) and Group (II) [$p < 0.001$]. There was no change in mean systolic BP in Group (II) (fig 3B). Diastolic BP rose significantly only in Group (I) [83 mm Hg ± 7 to 89 mm Hg ± 11: $p < 0.05$] (fig 4). There was no significant change in heart rate although resting heart rate was higher in Group (III) [$p < 0.01$].

Discussion

Studies on experimental postganglionic neuron section have given rise to the description of the phenomena of supersensitivity to sympathomimetic amines.[2 3] Two types of supersensitivity are described: "central" and "peripheral".[3] The central type or "decentralised

hypersensitivity" is known to be moderate in degree and relatively non-specific. It may be caused by any lesion of the proximal or pre-ganglionic pathway. The peripheral type, relevant to the present study, occurs after post-ganglionic section and is associated with an increased pressor response to noradrenaline and a reduced or absent response to tyramine. Peripheral supersensitivity has been demonstrated in chronic autonomic failure by Bannister *et al.*[4] The differential response with supersensitivity to noradrenaline and total loss of response to tyramine might only be expected if the postganglionic neuron section were complete.[4] Although tyramine stimulates noradrenaline release from the cytoplasmic pool at a sympathetic nerve terminal[5 6] and inhibits re-uptake of noradrenaline into sympathetic nerves,[7] it probably only releases small amounts of noradrenaline when autonomic dysfunction exists but there is both supersensitivity of and an increased number of receptors[2 8] on the effector cell. When considering central and peripheral supersensitivity it has to be borne in mind that the distinction between the two types may become confused as structural/functional changes may exist in both pathways.[4]

Our study has demonstrated for the first time an increased pressor response to intravenously infused noradrenaline in a group of patients with diabetic autonomic neuropathy as compared with a group of normal subjects or diabetic patients without neuropathy. In addition an increased pressor response to tyramine was also shown by the neuropaths. It was slightly surprising that tyramine at that rate of infusion did not produce an increase in blood pressure in the other two groups. We attributed this to the use of too low a dose of tyramine but nevertheless a clear-cut difference emerged between the neuropaths and the other two groups. Supersensitivity to both tyramine and noradrenaline in this context suggests that at least in the autonomic neuropaths that we studied the lesion is not complete post-ganglionic neuron destruction. A mixed pattern of damage in the post-ganglionic neuron seems more likely with reduction of nerve conduction and some preserved capacity to synthesise and store noradrenaline. It may be however, that if such studies were performed in autonomic neuropaths with more advanced disease that classical peripheral supersensitivity indicating complete post-ganglionic neuron destruction would be demonstrable.

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