Myasthenia gravis (MG) is characterized by a reduced number of acetylcholine receptors (AChR), which is adequate to account for the physiological abnormality. The immunoglobulin fraction of MG sera can passively transfer the disease in mice and plasma accelerates AChR degradation in cultured muscle and at the intact neuromuscular junction. As recently reported from this laboratory (Vincent, Scadding, Thomas, 1979), thymic lymphocytes from MG patients on prednisone and anticholinesterase alone but in no patient on azathioprine. The production of anti-AChR antibody in culture by peripheral blood lymphocytes from a proportion of MG patients provides a useful means of studying the disease process in MG and for investigating different forms of immunosuppressive treatment.

2. THE HYPOXIC DRIVE TO BREATHING IN DIABETIC AUTONOMIC NEUROPATHY

P. M. A. Calverley, I. W. Campbell, A. J. Ewing, P. K. Wraith, H. M. Brash, B. R. Clarke and D. C. Flenley

Department of Medicine and Diabetic Department, University of Edinburgh, The Royal Infirmary, Edinburgh, Scotland

Autonomic neuropathy is an important complication of diabetes associated with a significant mortality (Ewing, Campbell & Clarke, 1976, Lancet, i, 7960). An objective diagnosis is established by the presence of abnormal cardiovascular reflexes such as postural hypotension and abnormal response to a Valsalva manoeuvre or sustained handgrip. Recent reports of unexplained cardiorespiratory arrests in such patients (Page & Watkins, 1978, Lancet, i, 14) suggest that the control of ventilation may also be defective in these subjects. We have investigated this proposition.

We have studied five male patients with clinical autonomic neuropathy and abnormal cardiovascular reflexes and compared them with five control patients of similar age and duration of diabetes but without evidence of autonomic neuropathy. All patients were insulin-dependent diabetic subjects, stable at the time of assessment, and had normal ECG, FEV, FVC and lung volumes. After careful preliminary observation of their response to graded transient hypoxia each subject walked on a level treadmill at a constant speed for 30 min. The instantaneous minute ventilation, end tidal P02 and Pco2 were monitored before, during and after the administration of three breaths of nitrogen, this transient hypoxic stimulus being related to the transient ventilatory response. This transient response on exercise is presumed to measure the response of the carotid chemoreceptor (Calverley, Meddleton, Brash, Wraith & Flenley, 1977, Clinical Science and Molecular Medicine, 54, 189). Three such episodes of transient hypoxia were given during the walk and repeated in eight of the subjects (five control subjects and three patients with neuropathy), with the injection of controlled amounts of carbon dioxide into the inspired gas to maintain end-tidal Pco2 relatively constant during the response. There was no response to hypoxia in two of the control patients and in four of the subjects with autonomic neuropathy.

We conclude that transient hypoxia is a safe test of carotid chemoreceptor function in these patients and that the hypoxic ventilatory drive can be absent in patients with other features of autonomic neuropathy, but may also be absent in diabetic patients without such signs. Absence of normal chemoreceptor responsiveness to hypoxia may play a role in the cardiorespiratory arrests which are reported to occur in similar patients.

3. INHIBITION OF STEROL SYNTHESIS BY COMPACTIN IN FRESHLY ISOLATED LYMPHOCYTES AND INTESTINAL MUCOSA FROM NORMAL SUBJECTS AND PATIENTS HETEROZYGOUS FOR FAMILIAL HYPERCHOLESTEROLAEMIA

D. J. Betteridge, W. Krone, J. P. D. Reckless and D. J. Galton

Diabetes and Lipid Research Laboratory, St Bartholomew's Hospital, London

The serum cholesterol concentration is an important predictor for the development of atherosclerosis in the general population. A group particularly at risk from premature and extensive atherosclerosis are subjects with familial hypercholesterolaemia (FH). However, current therapeutic measures for treating hypercholesterolaemia are not satisfactory and new types of hypocholesterolaemic drugs are needed.

In mammalian cells the rate of cholesterol synthesis is determined by the activity of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) and attention has been focused on possible inhibitors of this enzyme. Recently compactin, a fungal metabolite of Penicillium brevibocktum, has been found to be a competitive inhibitor of HMG-CoA reductase.

We have measured the effect of compactin (a gift of Dr R. B. Fears of Beecham Pharmaceuticals) on sterol synthesis from [4C]acetate in freshly isolated human lymphocytes of normal subjects and patients heterozygous for FH. Compactin inhibited sterol synthesis from [4C]acetate by 65% at a concentration of 0.2 μM, inhibition being almost complete at 2 μM. In contrast to the incorporation of [4C]acetate, compactin did not affect the incorporation of [4C]-mevalonate into sterols, indicating that the drug is specifically inhibiting the activity of HMG-CoA reductase.

Compactin also inhibited sterol synthesis from labelled acetate in lymphocytes from patients with FH, the percentage inhibition being similar for a given concentration of the drug as compared with results for control subjects.