

the course of the disease. Combinations of cyclophosphamide, plasmapheresis, and steroids may also have short-term beneficial effects in MS.^{10,21} Unfortunately immunosuppressive drugs, particularly alkylating agents, have a close therapeutic/toxic ratio and a wide range of side-effects.²² Although long-term risks of malignant disorders in patients with non-neoplastic disease treated with immunosuppressive drugs are not precisely defined, alkylating agents such as cyclophosphamide have been associated with a higher than expected incidence of malignant disorders of the blood.¹⁹ Even less is known about long-term risks of immunosuppressive drugs in MS. However, in one MS study, a 2.5-fold increased risk of cancer was found in 131 patients treated with azathioprine for a mean of 6 years and malignant disorders occurred in almost 10% of the subgroup of MS patients followed 5 years or longer.²³ TLI seems not to be associated with a high risk of neoplasia and generally produces few serious side-effects in long-term follow-up.^{5,6}

TLI and immunosuppressive drugs in MS each have another theoretical advantage and disadvantage. By sparing the brain, TLI cannot damage its oligodendroglia, thereby allowing the possibility of remyelination, whereas immunosuppressive drugs which cross a normal or damaged blood-brain barrier might injure the oligodendroglia and inhibit remyelination. On the other hand, TLI does not eliminate immunocompetent cells in the brain; if MS is an autoimmune disease, these cells could continue to cause immune-mediated tissue injury for their lifetime in the CNS.

TLI therefore appears to be a promising new therapy for the treatment of patients with chronic progressive MS. However, amplification of our results is needed before the overall efficacy of TLI in MS can be judged and the subgroups of patients who might most benefit identified. In the mean time, TLI should be considered an experimental therapy in MS patients and its use in this disorder restricted to MS study groups.

Addendum

Subsequent to completion of this study, 1 severely disabled MS patient, 3 years after TLI, died from a flu-like syndrome complicated by staphylococcal pneumonia, obstruction of her endotracheal tube, and cardiorespiratory arrest.

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REFERENCES

1. Slavin S, Strober S, Fuks Z, Kaplan HS. Induction of specific tissue transplantation tolerance using fractionated total lymphoid irradiation in adult mice: long-term survival of allogeneic bone marrow and skin grafts. *J Exp Med* 1977; **146**: 34-48.
2. Kotzin BL, Strober S. Reversal of NZB/NZW disease with total lymphoid irradiation. *J Exp Med* 1979; **150**: 371-78.
3. Kotzin BL, Stober S, Engleman EG, et al. Treatment of intractable rheumatoid arthritis with total lymphoid irradiation. *N Engl J Med* 1981; **305**: 969-76.
4. Trentham DE, Belli JA, Anderson RJ, et al. Clinical and immunologic effects of fractionated total lymphoid irradiation in refractory rheumatoid arthritis. *N Engl J Med* 1981; **305**: 976-82.
5. Field EH, Strober S, Hoppe RT, et al. Sustained improvement of intractable rheumatoid arthritis after total lymphoid irradiation. *Arthritis Rheum* 1983; **26**: 937-46.
6. Hafstein MP, Devereux C, Troiano R, et al. Total lymphoid irradiation in chronic progressive multiple sclerosis: a preliminary report. *Ann NY Acad Sci* 1984; **436**: 397-409.
7. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; **13**: 227-31.

EVIDENCE FOR DOWN-REGULATION OF BETA-2-ADRENOCEPTORS IN CIRRHOTIC PATIENTS WITH SEVERE ASCITES

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Summary The density and affinity of beta-2-adrenoceptors on mononuclear cells from peripheral blood were studied in fifteen patients with cirrhosis of different severity and in thirteen controls. There was no significant difference between cirrhotic patients and controls in density or affinity of beta-2 binding sites. Within the cirrhotic group, however, the number of binding sites per cell was significantly lower in patients with severe ascites than in patients with mild to moderate or no ascites. This down-regulation of beta-adrenoceptors could influence the haemodynamic response to beta-blockers.

Introduction

LEBREC and colleagues^{1,2} found that the non-selective beta-adrenoceptor blocker propranolol reduced the frequency of gastrointestinal rebleeding in patients with cirrhosis and oesophageal varices, but this finding was not confirmed by Burroughs et al.³ This discrepancy might be due to differences in the severity of cirrhosis in the selected patients, since the stage of liver disease influences the haemodynamic effects of propranolol.⁴

S. D. COOK AND OTHERS: REFERENCES—continued

8. Cook SD, Dowling PC. Multiple sclerosis and viruses: an overview. *Neurology* 1980; **30**: 80-91.
9. Bauer HJ, Firnhaber W, Winkler W. Prognostic criteria in multiple sclerosis. *Ann NY Acad Sci* 1965; **122**: 542-51.
10. Hauser SL, Dawson DM, Leichner JR, et al. Intensive immunosuppression in progressive multiple sclerosis. A randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Engl J Med* 1983; **308**: 173-80.
11. Schettler L, Shealy NC. Experimental selective alteration of the blood-brain-barrier by x-irradiation. *J Neurosurg* 1970; **32**: 89-94.
12. Oldendorf WH, Cornford EM. A comparison of total body and local spinal cord irradiation in experimental allergic encephalomyelitis. *J Neuropathol Exp Neurol* 1977; **36**: 50-61.
13. Tourtellotte WW, Porvin AR, Baumhefner RW, et al. Multiple sclerosis de novo CNS IgG synthesis. Effect of CNS irradiation. *Arch Neurol* 1980; **37**: 620-24.
14. Mastaglia FL, McDonald WI, Watson JV, Yogendran K. Effects of X-radiation on the spinal cord: an experimental study of the morphological changes in central nerve fibers. *Brain* 1976; **99**: 101-22.
15. Paterson PY, Richardson WP, Drobish DG. Cellular transfer of experimental allergic encephalomyelitis: altered disease pattern in irradiated recipient Lewis rats. *Cell Immunol* 1975; **16**: 48-59.
16. Fuks Z, Strober S, Bobrove AM, Sasazuki T, McMichael A, Kaplan HS. Long-term effects of radiation on T and B lymphocytes in peripheral blood of patients with Hodgkin's disease. *J Clin Invest* 1976; **58**: 803-14.
17. Rose AS, Kuzma JW, Kurtzke JF, Namerow NS, Sibley WA, Tourtellotte WW. Cooperative study in the evaluation of therapy in multiple sclerosis: ACTH vs placebo: final report. *Neurology* 1970; **20**: 1-59.
18. Dowling PC, Bosch VV, Cook SD. Possible beneficial effect of high dose intravenous steroid therapy in acute demyelinating disease and transverse myelitis. *Neurology* 1980; **30**: 33-36.
19. Troiano R, Hafstein M, Ruderman M, Dowling P, Cook SD. Effect of high-dose intravenous steroid administration on contrast-enhancing computed tomographic scan lesions in multiple sclerosis. *Ann Neurol* 1984; **15**: 257-63.
20. Sowa K, Hamaguchi K, Ohno R, Tanaka H. High dose intravenous corticosteroids treatment in multiple sclerosis. *J Neurol* 1985; **232** (suppl): 123.
21. Khatri BO, McQuillen MP, Harrington GJ, Schmoll D, Hoffmann RG. Chronic progressive multiple sclerosis: double-blind controlled study of plasmapheresis in patients taking immunosuppressive drugs. *Neurology* 1985; **35**: 312-19.
22. Kaplan SR, Calabresi P. Drug therapy. Immunosuppressive agents. *N Engl J Med* 1983; **289**: 952-54.
23. Lhermitte F, Marteau R, Roulet E. Not so benign long-term immunosuppression in multiple sclerosis. *Lancet* 1984; **i**: 276-77.

Thus, the severity of cirrhosis might affect the density or affinity of beta-adrenoceptors. We have studied beta-adrenoceptor status in patients with cirrhosis of different severity.

Subjects and Methods

We compared fifteen cirrhotic patients, ten men and five women, aged 41–76 years (median 56 years), three grade A, nine grade B, three grade C by a modified Child classification,^{5,6} and thirteen controls, seven men and six women, aged 36–81 years (median 55 years). No subject was receiving drugs for treatment of the cardiovascular system. Most of the patients were taking antacids, diuretics (spironolactone 0–400 mg daily, or frusemide 0–80 mg daily), vitamin K, and lactulose. The severity of ascites was determined by physical examination and ultrasound the day before the receptor status determinations. Clinical and laboratory data were collected independently by different physicians and treated separately until statistical analysis.

Mononuclear cells were separated from samples of peripheral blood taken in the morning by means of 'Ficoll-Hypaque' (Pharmacia, Heidelberg).⁷ There is evidence that the beta-2-adrenoceptors on these lymphocytes and monocytes represent those in other organs,^{8,9} and these readily available cells are commonly used for beta-2-adrenoceptor investigations.^{10,11} Specific binding of iodine-125-labelled cyanopindolol (2100 Ci/mmol, Amersham) was measured by incubating 1 ml cell suspension (5×10^5 cells) at 37°C for 90 min with or without 0.1 $\mu\text{mol/l}$ timolol. Incubation was ended by centrifugation at 18 000 *g*. At least eight different ligand concentrations were used for determining the receptor status of each subject. Density of binding sites (B_{max}) and apparent equilibrium dissociation constant (K_d), as an indicator of affinity were calculated according to Scatchard.¹² Statistical significance was determined by the two-tailed Mann-Whitney test; a *p* value less than 0.05 was considered significant. Correlations were analysed by polynomial regression.

Results

There were no significant differences between the cirrhotic patients and the controls in B_{max} (509–1958, median 1035, *vs* 595–2120, median 1034, binding sites per cell) or K_d (1.8–5.3, median 2.7×10^{-12} mol/l *vs* 1.6–8.6, median 4.1×10^{-12} mol/l). Neither age nor sex was correlated with B_{max} or K_d in either group. The heart rate in cirrhotic patients (76–100, median 84 beats/min) was significantly higher than that in controls (60–88, median 68 beats/min). This elevation, possibly indicating increased adrenergic activity of the beta-1-adrenoceptors, was not correlated with the density of beta-2-adrenoceptors. Furthermore, in the cirrhotic patients no correlation was found between beta-receptor status and the dosage of various drugs, particularly the extent of diuretic treatment, or several indicators of the severity of liver disease, such as serum bilirubin, serum albumin, prothrombin time, and Child-Pugh score. There was no significant correlation between B_{max} and plasma potassium in patient or control group. However, there was a significant ($p < 0.01$) negative correlation ($r = -0.73$) between the density of binding sites and the grade of ascites defined by physical examination and ultrasound (fig 1). The reduced receptor density and unchanged affinity in a representative cirrhotic patient with severe ascites are shown in fig 2.

Discussion

In view of the high plasma catecholamine levels reported in decompensated cirrhosis,^{13,14} the reduction in beta-2-adrenoceptors in cirrhotic patients with severe

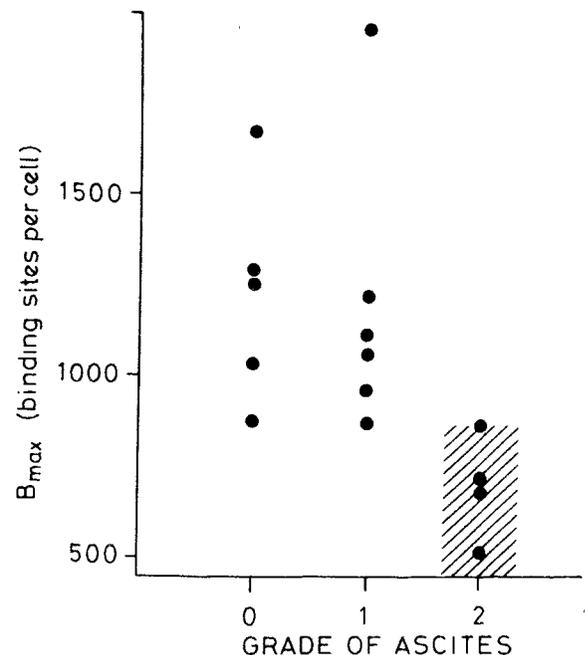


Fig 1—Density of beta-2-adrenoceptors in cirrhotic patients with no ascites (grade 0), mild to moderate (grade 1) ascites, or severe (grade 2) ascites.

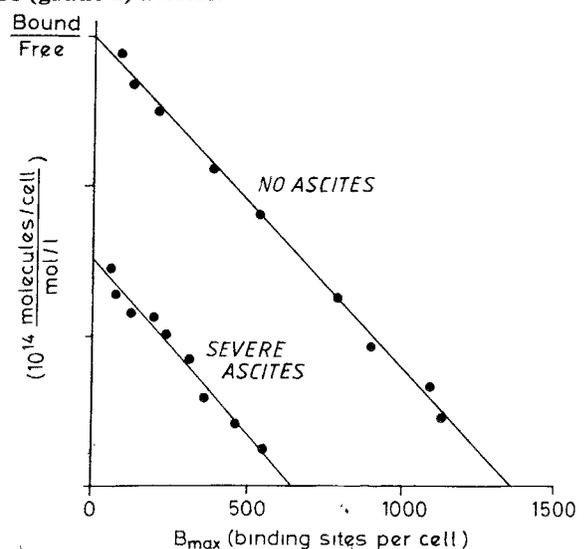


Fig 2—Representative Scatchard plots of one patient with no ascites and one patient with severe ascites.

ascites can be interpreted as down-regulation. Down-regulation of beta-adrenoceptor density can be assumed to affect the haemodynamic response to beta-blocking drugs. This finding is particularly interesting, since selective beta-2 blockade is being recommended as pharmacological treatment in portal hypertension.^{15–17} Because of the pronounced differences in receptor density between individuals, the determination of beta-adrenoceptor status might prove useful in selecting the appropriate dose¹⁸ of beta-blocking agents. Finally, our findings could offer an explanation for the discrepant results of propranolol treatment for prevention of recurrent gastrointestinal bleeding;^{2,3} patients with severe cirrhosis and severe ascites, included in Burroughs'³ but not in Lebrec's² study, may have shown less response to propranolol owing to down-regulation of beta-2-adrenoceptors.

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