The role of the false neurotransmitter octopamine in the hypotension of fulminant hepatic failure

P. N. TREWBY, R. A. CHASE, M. DAVIS AND R. WILLIAMS
Liver Unit, King's College Hospital and Medical School, London

(Received 20 May 1976; accepted 22 October 1976)

Summary

1. An investigation was carried out into the mechanism of unexplained hypotension in patients with fulminant hepatic failure. The cardiac output and peripheral resistance were compared in normotensive and hypotensive patients. In addition, the serum concentration of the false neurotransmitter octopamine and the pressor response to noradrenaline, and to the indirectly acting sympathomimetic agent tyramine, were measured in hypotensive and normotensive patients with fulminant hepatic failure and in healthy subjects.

2. The cardiac output and the peripheral resistance were decreased in the hypotensive patients, and their mean heart rate was slower than in the normotensive patients. Although the serum octopamine concentration was significantly elevated in the patients compared with the control subjects, the highest octopamine concentrations were unexpectedly found in the normotensive patients and a significant positive correlation could be demonstrated between the resting blood pressure and the serum octopamine concentration. The pressor response to tyramine and noradrenaline were similar in the hypotensive patients, the normotensive patients and control subjects.

3. These results suggest that neither increased serum concentrations of the false neurotransmitter octopamine, nor end-organ insensitivity to released noradrenaline are responsible for the hypotension. A more likely explanation is toxic depression of the vasomotor centre. The opening of peripheral arteriovenous shunts, possibly as a result of endotoxaemia, might be an additional factor.

Key words: fulminant hepatic failure, haemodynamics, hypotension, octopamine.

Introduction

Hypotension which is not due to blood loss commonly occurs in fulminant hepatic failure (Rueff & Benhamou, 1973; Ritt, Whelan, Werner, Eigenbrodt, Schenker & Combes, 1969) and may lead to secondary hypoxic brain damage as well as further impairment of hepatic and renal function. One suggested mechanism for its occurrence is the accumulation at sympathetic nerve terminals of false neurotransmitters, such as octopamine (Fischer & Baldessarini, 1971). Octopamine is derived from the β-hydroxylation of tyrosine and phenylalanine, the serum concentrations of which are known to be raised in fulminant hepatic failure (Record, Chase, Curzon & Murray-Lyon, 1975). Like noradrenaline, it can be taken up by, and released from, sympathetic nerve terminals but, on a molar basis, possesses only 1% of noradrenaline’s pressor activity (Lands & Grant, 1952).

In this investigation, in addition to measurements of the serum octopamine and the systemic peripheral resistance, we have determined the pressor response to infusions of tyramine, which releases both true and false neurotransmitters from sympathetic nerve endings (Kopin, Fischer, Musacchio, Horst & Weise, 1965). The sensitivity of the peripheral vessels

305
in these patients to released noradrenaline was also assessed by measuring the pressor response to infusions of noradrenaline.

**Patients and methods**

The 23 patients investigated were in grade IV coma (Trey & Davidson, 1970) due to fulminant viral hepatitis. Twelve patients had acute viral hepatitis, and three of these had hepatitis-B antigen (HBsAg) in their serum. There were two patients with halothane-associated liver damage, the remaining nine having taken a paracetamol overdose with suicidal intent.

Venous blood was taken for octopamine assay from 17 of these patients.

The serum octopamine was assayed according to the method of Molinoff, Landsberg & Axelrod (1969), as modified by Lam, Tall, Goldstein & Mistilis (1973), in which the $^{14}$C-labelled methyl group of $S$-adenosyl methionine is transferred to octopamine by the use of phenylethanolamine-N-methyltransferase. Plasma (0.4 ml) was used for each determination and the methylated product was extracted into toluene/isoamyl alcohol (3:2, v/v) and the radioactivity in the organic phase was counted in a Packard Tricarb scintillation counter (counting efficiency greater than 80%).

Three test samples of serum and two control samples were run in parallel for each octopamine estimation. The test samples contained 0, 0.065 and 0.130 nmol of octopamine as internal standards, and the two control samples consisted of the complete system without phenylethanolamine-N-methyltransferase and the complete system without $S$-adenosylmethionine. Solvent extracts of plasma were subjected to thin-layer chromatography with two solvent systems (butan-1-ol/acetic acid/water, 4:4:1, by vol., and benzene/propionic acid/water, 10:9:1, by vol.). Two compounds were identified, one of which was shown to be unchanged $S$-adenosylmethionine and the other methylated octopamine. Test plasma samples containing non-methylated octopamine and noradrenaline were found to have different $R_f$ values from methylated octopamine when subjected to this solvent system. The lower limit of sensitivity of the assay was found to be 0.0039 nmol/sample.

The cardiac output was measured immediately after blood had been taken for octopamine assay, either by dye dilution with Indocyanine Green (five studies) (Hamilton, 1962) or thermodilution (Ganz & Swan, 1962) with a Swan-Ganz pulmonary artery thermodilution catheter (12 studies). For each cardiac output determination the mean of three readings was taken. Determinations were discarded if the individual readings varied by more than 0.51/ min. The indexed systemic peripheral resistance was calculated from the equation (Wood, 1956):

$$\text{Indexed peripheral resistance} = \frac{\text{Mean blood pressure (mmHg)} \times 0.133}{\text{Cardiac index (l min}^{-1} \text{ m}^{-2})} \text{kPa l}^{-1} \text{ min}^{-2}$$

Blood pressure was measured by sphygomonomanometry and the mean blood pressure (mmHg) was calculated as diastolic blood pressure $+\frac{1}{3}$ pulse difference.

On a separate occasion the pressor response to injected tyramine was measured in 18 patients by injecting doses of 3, 6 and 9 mg of tyramine (21.9, 43.8 and 65.7 pmol) into a fast-running intravenous infusion of 5% glucose solution and measuring the blood pressure by sphygmomanometry every 20 s. The peak systolic blood pressure for each dose was recorded and compared with the blood pressure during infusion of glucose alone. A delay of 5 min was allowed between the blood pressure falling to normal and the next dose of tyramine. After completion of this procedure, noradrenaline was injected in doses of 3, 6 and 9 $\mu$g (17.7, 35.5 and 53.2 nmol) and the pressor response determined in the same way. If, after the first injection of either drug, the blood pressure rose by more than 10 mmHg subsequent doses were reduced so that the maximum rise in blood pressure with the largest dose did not exceed 30 mmHg. For each patient a four-point dose–response curve was constructed for both tyramine and noradrenaline. The gradients of the curves were determined by linear regression, and the pressor response was expressed for each patient as change in systolic blood pressure (mmHg) kg$^{-1}$ body weight $\mu$mol$^{-1}$ of tyramine or nmol$^{-1}$ of noradrenaline.

Ten age- and sex-matched healthy subjects with no history of heart or liver disease served as controls for the serum octopamine concentration, the resting blood pressure, and the tyramine and noradrenaline pressor responses.
Octopamine in hypotension of hepatic failure

The values for cardiac index and peripheral resistance obtained in the patients with fulminant hepatic failure were compared with previously reported results in healthy subjects by indicator dilution techniques (Doyle, Wilson, Lepine & Warren, 1953; Carey, Brown, Mohr, Monson, Yao & Shoemaker, 1967).

Statistical analyses were performed with Student's t-test. Results are expressed as the mean value ± 1 SEM.

Permission was obtained from the local ethical committee for performing all these investigations and informed consent obtained from the patient's relatives and the normal subjects.

Results
Seventeen of the 23 patients became hypotensive at some stage of their illness with a systolic blood pressure less than 80 mmHg not accounted for by haemorrhage or sepsis. When hypotensive no patient had PaO₂ of less than 10 kPa and, in addition, plasma sodium and potassium concentrations were within normal limits at the time of investigation. Once hypotension had occurred the prognosis was poor, with only one of these patients recovering consciousness, whereas five of the six patients who remained normotensive throughout their illness recovered consciousness.

Values for peripheral resistance were reduced in all patients in whom it was measured, but were significantly lower in the hypotensive than the normotensive group (Table 1).

With one exception, values for cardiac index in the hypotensive patients fell within the normal range. That patient had a cardiac index of 1.7 1 min⁻¹ m⁻² and had been hypotensive for 14 h before investigation with ischaemic changes on electrocardiogram. The cardiac index in the hypotensive patients was, however, significantly lower than in the normotensive patients (Table 1).

Despite their low blood pressure, compensatory tachycardia was not observed in the hypotensive patients. Indeed their mean heart rate was significantly slower than that in the normotensive patients (93.7 ± 5.0/min and 108.7 ± 3.3/min respectively; P < 0.02).

Serum octopamine concentrations were raised in both normotensive and hypotensive patients, with a mean value for the complete group of 17.63 nmol ± 0.85 as compared with 11.43 ± 1.24 nmol/l in the control subjects (P < 0.001).Unexpectedly the highest concentrations were found in the normotensive, rather than the hypotensive, patients (Table 1) and a significant positive correlation was found between the blood pressure and the serum octopamine concentration (Fig. 1).

The pressor response to tyramine measured in 19 patients did not differ significantly from control subjects, with values of 68.3 ± 10.9 and 57.1 ± 3.9 mmHg kg⁻¹ µmol⁻¹ of tyramine respectively. When separated into those patients

<table>
<thead>
<tr>
<th>Table 1. Relation between serum octopamine concentration, cardiac index and peripheral resistance in the normotensive and hypotensive patients with fulminant hepatic failure and control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values are mean ± 1 SEM. P values refer to differences from normal control subjects. In addition there was a significant difference in the peripheral resistance (P &lt; 0.005) and the serum octopamine concentration (P &lt; 0.02) between the normotensive and hypotensive patients.</td>
</tr>
<tr>
<td>Healthy control subjects</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
</tr>
<tr>
<td>Indexed peripheral resistance (kPa min⁻¹ m⁻²)</td>
</tr>
<tr>
<td>Cardiac index (1 min⁻¹ m⁻²)</td>
</tr>
<tr>
<td>Serum octopamine (nmol/l)</td>
</tr>
</tbody>
</table>

* Control values for indexed peripheral resistance from Carey et al. (1967).
† Control values for cardiac index from Doyle et al. (1953).
with systolic blood pressures of less than 80 mmHg and those greater than 80 mmHg there was still no difference in mean pressor response between the two groups and the control subjects (Fig. 1). Although there was a much wider distribution of results in the patients than in the control subjects, the highest pressor response was found in a hypotensive patient.

The pressor response to noradrenaline was not found to differ significantly between the control subjects, the normotensive patients and the hypotensive patients, with values of $47.8 \pm 10.1$, $33.6 \pm 8.6$ and $40.9 \pm 8.8$ mmHg kg$^{-1}$ nmol$^{-1}$ of noradrenaline (Fig. 2).

The coefficient of correlation between dose of tyramine and pressor response was greater than 0.90 in all patients and control subjects and for noradrenaline greater than 0.85.

**Discussion**

The poor prognosis associated with hypotension in fulminant hepatic failure is not surprising. The hypotension may not only have been a reflection of more severe hepatic necrosis but also, by reducing cerebral, as well as hepatic, myocardial and renal perfusion, could lead to further hypoxic damage to these organs.

The combination of a low peripheral resistance and a normal cardiac output suggests that inappropriate vasodilatation rather than primary myocardial pump failure was the cause of the hypotension. Even though the serum octopamine concentration was increased,
it seems highly improbable that raised levels are the cause of the hypotension since the highest octopamine concentrations were found in those patients with a normal blood pressure. The positive correlation between the resting blood pressure and the serum octopamine concentration could be explained if octopamine were being released together with noradrenaline from sympathetic nerve terminals and if sympathetic activity was increased in the normotensive compared with the hypotensive patient. Increased sympathetic activity would explain the high cardiac output found in the normotensive patients as well as their tachycardia, and diminished sympathetic drive in the hypotensive patients would be compatible with their inappropriate bradycardia and decreased peripheral resistance. Serial measurements of serum noradrenaline concentration simultaneously with octopamine concentration would therefore be of considerable interest.

The normal pressor response to tyramine in hypotensive, as well as in normotensive, patients also supports the hypothesis that neither octopamine nor other false neurotransmitters such as phenylethanolamine are directly responsible for the hypotension. Tyramine releases both noradrenaline and false neurotransmitters from sympathetic nerve terminals (Kopin et al., 1965) but has no intrinsic sympathomimetic activity (Burn & Rand, 1958). In the presence of significant sympathetic blockade from false neurotransmitters a diminished pressor response would therefore have been expected and this was not found. The normal pressor response to noradrenaline suggests no abnormality in end-organ response to released noradrenaline nor significant depletion of noradrenaline stores. The latter would be expected to result in an increased response to infused noradrenaline (Burn & Rand, 1958) and this did not occur. In contrast, Mashford, Mahon & Chalmers (1962) have demonstrated that hypotensive patients with decompensated cirrhosis exhibit a decreased tyramine pressor response and a heightened noradrenaline response, suggesting that noradrenaline depletion may play a role in the hypotension of chronic liver disease.

What then is the cause of the decreased peripheral resistance and hypotension of fulminant hepatic failure? Diminished sympathetic drive secondary to toxic depression to the brain-stem vasomotor centre could account for our findings. Ammonia, non-esterified fatty acids and mercaptans are recognized central depressants whose plasma concentrations are known to be raised in fulminant hepatic failure (Schenker, Breen & Hoyumpa, 1974). Compression of the brain stem secondary to cerebral oedema could also result in damage to the vasomotor centre. In a recent autopsy study (Gazzard, Portmann, Murray-Lyon & Williams, 1975) cerebral oedema was found in 38% of patients dying from fulminant hepatic failure. In addition, endotoxaemia, which in an earlier study (Wilkinson, Arroyo, Gazzard, Moodie & Williams, 1974) was found in 64% of patients with fulminant hepatic failure, may exacerbate the fall in peripheral resistance. Experimental injection of endotoxin leads to vasodilatation, and the opening of peripheral arteriovenous shunts (Liehr, Grün, Thiel, Brunswig & Rasenack, 1975), and in this respect it is noteworthy that we have recently demonstrated intrapulmonary shunts of up to 39% of the cardiac output in patients with fulminant hepatic failure with a corresponding increase in peripheral shunting as assessed by the arteriovenous oxygen content difference (Trewby, Williams, Williams & Reid, 1976). If central vasomotor depression were combined with peripheral arteriovenous shunting then a considerable fall in blood pressure would be expected.

Acknowledgments

This study is part of a programme of research in liver failure supported by the Medical Research Council, Smith's Charity and the Wates' Foundation.

References


