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COMMUNICATIONS

Can the alterations in serum glucocorticoid concentrations explain the effects of ethanol and benfluorex on the synthesis of hepatic triacylglycerols?

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PAP (Phosphatidate phosphohydrolase; EC 3.1.3.4) appears to have a regulating function in hepatic TG (triacylglycerol) synthesis and glucocorticoids seem to be important in its control (Brindley 1978; Glenny & Brindley 1978; Brindley et al 1979a,b; Lehtonen et al 1979). Ethanol consumption promotes the release of glucocorticoids into the circulation (Mendelson 1971), and increases the hepatic activity of PAP (Savolainen 1977; Pritchard et al 1977; Sturton et al 1978; Lamb et al 1979). Furthermore, an intact pituitary-adrenal axis is necessary for ethanol to produce a fatty liver (Mallov & Bloch 1956; Brodie & Maickel 1963; Maickel & Brodie 1963; Maling et al 1963) and adrenalectomizing rats inhibits more than 85% of the ethanol-induced increase in hepatic PAP activity (Brindley et al 1979a). Chronic treatment of rats with benfluorex also substantially decreases the effect of ethanol in stimulating the synthesis and accumulation of triacylglycerols (Pritchard & Brindley 1977), and the activity of PAP (Pritchard et al 1977) in the liver. Conversely, treating rats with a single dose of benfluorex appears to promote hepatic TG synthesis (Brindley et al 1976). We therefore predicted that these effects of benfluorex on TG metabolism might be mediated indirectly through altering the metabolism of glucocorticoids. The work presented was designed to test this hypothesis.

Rats were given benfluorex in a single dose of 50 mg kg^{-1} by stomach tube (Brindley et al 1976) and the concentrations of circulating corticosterone and insulin were measured 3 h later (Brindley et al 1979a). This is the time when the effects of benfluorex on hepatic lipid metabolism were measured in previous experiments (Brindley et al 1976). The concentration of insulin was measured since it antagonizes many of the effects of glucocorticoids. Acute treatment of four rats with benfluorex increased ($P < 0.01$) the corticosterone concentrations in the sera to 243 $\pm$ 72 μg $litre^{-1}$ (mean $\pm$ s.e.m.) compared with 79 $\pm$ 14 μg $litre^{-1}$ in four control rats that were fed gum tragacanth suspension. The concentrations of insulin in the sera of these benfluorex-treated and control rats were 71 $\pm$ 14 and 65 $\pm$ 4·5 mU $litre^{-1}$ respectively, and these results were not significantly different.

The mean concentration of circulating corticosterone in the chronically treated benfluorex group was about 3-fold less ($P < 0.05$) than that in the group treated acutely with benfluorex (Table 1). It was about 2-fold higher than that in the chronically treated controls, but this difference was not statistically significant ($0.1 > P > 0.05$) with the number of rats used. The concentrations of circulating insulin were not significantly altered (Table 1).

Feeding ethanol to the control rats increased the concentration of serum corticosterone and this was maximum at 3 h after feeding (Table 1). At 6 h after feeding the concentration of corticosterone in the control rats given ethanol was similar to that in the control rats fed glucose. The rats that had been dosed with benfluorex had similar concentrations of corticosterone in their sera at 1·5 h after ethanol feeding to those of the control rats fed ethanol (Table 1). At 3 h after feeding ethanol this concentration in the benfluorex group (III) was about half ($P < 0.01$) that in the controls that received ethanol (II) and about 2-fold higher than that in the benfluorex treated rats that were fed glucose (IV). However, the difference in the latter case was not statistically significant ($0.1 > P > 0.05$). The results in Table 1 show that treatment with benfluorex interferes with the metabolism or release of corticosterone after ethanol feeding, since we already know that this treatment does not alter the rate of ethanol absorption, or its oxidation to CO_2 (Pritchard & Brindley 1977).

Feeding glucose to rats also increases ($P < 0.05$) the concentrations of circulating corticosterone, but this is more transient than that produced by ethanol and it is accompanied by an increase in circulating insulin (Table 1; Brindley et al 1979a). Glucose feeding, in contrast to that of ethanol, does not increase the activity of PAP in the liver (Savolainen 1977; Sturton et al 1978).

The results presented are compatible with the hypothesis that chronic benfluorex treatment decreases the

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Table 1. Effect of ethanol on the concentration of corticosterone and insulin in the sera of rats that had been treated for five days with benfluorex. Rats were treated daily for 5 days with benfluorex or with gum tragacanth suspension (controls) and they were fed 2 h after the fifth dose of drug with ethanol or isocaloric glucose (Pritchard & Brindley 1977). The serum concentrations of corticosterone and insulin were measured and the results are expressed as means ± s.e.m. The number of rats is shown in parentheses and the significance of the difference between groups is indicated by: $*P < 0.01$; $\dagger P < 0.001$.

Hormone	Time after feeding ethanol or glucose	(I) Control + glucose	(II) Control + ethanol	(III) Benfluorex + ethanol	(IV) Benfluorex + glucose
Corticosterone (μg litre^{-1})	0 h	32 ± 6 (4)	32 ± 6 (4)	68 ± 18 (4)	68 ± 18 (4)
	1·5 h	131 ± 36 (5)	169 ± 9 (5)	175 ± 7 (5)	211 ± 43 (5)
	3 h	82 ± 20 (8) I vs II†	251 ± 27 (8) II vs III*	125 ± 35 (7)	53 ± 9 (7)
	6 h	80 ± 19 (5)	93 ± 18 (5)	91 ± 47 (4)	108 ± 15 (5)
Insulin (mU litre^{-1})	0 h	83 ± 11 (4)	83 ± 11 (4)	69 ± 13 (4)	69 ± 13 (4)
	1·5 h	132 ± 6 (5) I vs II*	105 ± 6 (5)	85 ± 11 (5)	113 ± 12 (5)
	3 h	140 ± 18 (3)	104 ± 6 (3)	115 ± 17 (3)	89 ± 17 (3)
	6 h	143 ± 26 (5)	119 ± 15 (5)	122 ± 21 (4)	131 ± 15 (5)

extent and duration of the ethanol-induced increase in circulating glucocorticoids in rats, and that this partially prevents the stimulation of hepatic TG synthesis by ethanol. Benfluorex did not appear to significantly decrease the transient increase in circulating glucocorticoids produced by glucose. The effects of benfluorex on glucocorticoid metabolism could augment any direct effects that it might have on PAP activity (Brindley et al 1978), and the indirect effects might contribute to the observed actions of benfluorex on carbohydrate and lipid metabolism (Duhault et al 1976; Brindley et al 1979c).

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