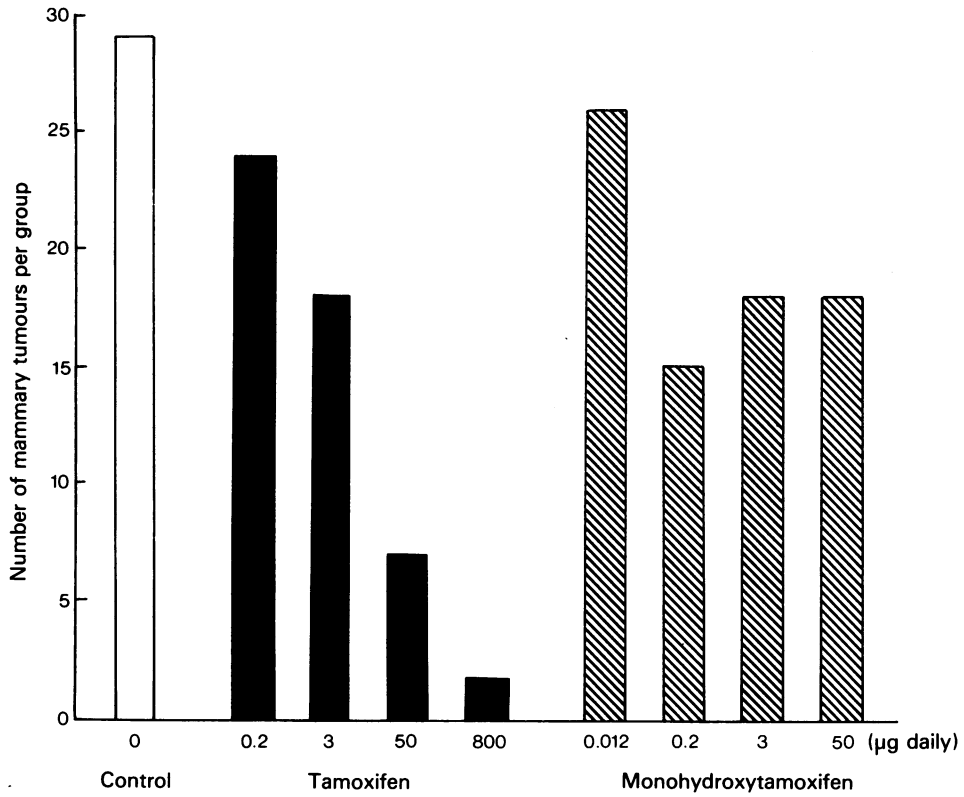

Figure 1 The incidence of mammary tumours in groups of rats (15 per group) 11 weeks after receiving different daily doses of tamoxifen or monohydroxytamoxifen. Antioestrogen treatment was instituted 30 days after carcinogen (DMBA) administration and was continued for 30 days. Controls received injection vehicle alone.

References

JORDAN, V.C. (1976a). Effect of tamoxifen (ICI 46,474) on initiation and growth of DMBA-induced rat mammary carcinomata. *Europ. J. Cancer*, 12, 419–424.

JORDAN, V.C. (1976b). Antiestrogenic and antitumour properties of tamoxifen in laboratory animals. *Cancer Treat. Rep.*, **60**, 1409–1419.

JORDAN, V.C., COLLINS, M.M., ROWSBY, L. & PRESTWICH, G. (1977). A monohydroxylated metabolite of tamoxifen with potent antioestrogenic activity. *J. Endocr.*, **75**, 305–316.

A mechanism by which fenfluramine and benfluorex could inhibit the synthesis of triacylglycerols

D.N. BRINDLEY, P.H. PRITCHARD & R.G. STURTON
(introduced by A.T. BIRMINGHAM)

Department of Biochemistry, University Hospital and Medical School, Clifton Boulevard, Nottingham NG7 2UH, U.K.

The ability of drugs to inhibit the synthesis of triacylglycerols could be important in preventing the accumulation of fat in obesity. Such drugs could inhibit the excessive secretion of very low density lipoproteins and thus also indirectly decrease the production of low density lipoproteins. They might also be useful biochemical tools for studying the mechanisms that control triacylglycerol synthesis.

The most important regulatory enzyme in this process appears to be phosphatidate phosphohydrolase (EC 3.1.3.4) (Brindley, 1978). One of the best ways to exert pharmacological control is to alter the activity of regulatory enzymes. Amphiphilic cationic compounds, such as fenfluramine and benfluorex, interact physically with phosphatidate and prevent the action of the phosphohydrolase *in vitro*. There is evi-

dence that this inhibition also occurs *in vivo*, and these compounds are particularly interesting since they are used to treat obesity and hyperlipidaemia respectively.

Chronic treatment of rats with benfluorex before feeding with glucose decreased the relative rate of hepatic triacylglycerol synthesis. This effect was more marked if the rats were fed with ethanol which increases the activity of phosphatidate phosphohydrolase in the liver by about 5-fold. Benfluorex partly prevents the ethanol-induced increase in the synthesis and accumulation of triacylglycerols in the liver which appears to be caused by the increased flux of phosphatidate to diacylglycerol. Benfluorex could decrease this flux by interacting with phosphatidate, but it also partly prevents the ethanol-induced increase in the concentration of active phosphohydrolase (Brindley, 1978).

If triacylglycerol synthesis can be inhibited by restricting the conversion of phosphatidate to diacylglycerol, then phosphatidate ought to accumulate. This occurs to a limited extent and some of the phosphatidate can be used for acidic phospholipid synthesis (Brindley, 1978). It appears likely that most of the excess phosphatidate in the liver is converted back to glycerol phosphate. Toxic doses of amphiphilic amines inhibit phospholipase A activities and produce a phospholipidoses (Brindley, 1978), but lower concentrations could favour the deacylation of phosphatidate relative to its dephosphorylation. Norfenfluramine (2 mM) and chlorpromazine (0.8 mM) inhibited phosphatidate phosphohydrolase activity by 13 and 81% respectively. The simultaneous deacylation was increased by 24% with norfenfluramine and it was only decreased by 26% with chlorpromazine. These results were obtained with a microsomal plus supernatant fraction of rat liver that was labelled with [^{3}H]-phosphatidate in the membranes.

Reference

BRINDLEY, D.N. (1978). Some aspects of the physiological and pharmacological control of the synthesis of triacylglycerols and phospholipids. *Int. J. Obesity*, **2**, 7–16.

Feeding parameters in the rat: interactions of chlordiazepoxide with (+)-amphetamine or fenfluramine

S.J. COOPER & R.L. FRANCIS

Department of Psychology, The Queen's University of Belfast, Belfast BT7 1NN Northern Ireland

Benzodiazepines can antagonize amphetamine-induced anorexia (Cooper, in press; Fratta, Mereu, Chessa, Paglietti & Gessa, 1976), but interactions with fenfluramine have not been investigated. Typically food intake data is restricted to the amount of food consumed; in the present study, the amount of food intake was subdivided into two feeding parameters, feeding duration and rate of eating. Here we report on interactions between chlordiazepoxide with either (+)-amphetamine or fenfluramine on feeding parameters in the rat.

Male, adult Sprague-Dawley rats (240–280g) were handled daily for 8 days prior to testing. On the day before testing, food (Diet 41B pellets) were removed at 17.00 h, and feeding tests were run the following morning. Each rat was tested for 10 min in a test-cage, similar to the home-cage, with familiar food pellets available (to avoid neophobic responses). The measures taken were latency to begin feeding (s); total duration of feeding (s); amount consumed (g); eating rate (g per 100s feeding). 120 rats were allocated to 15 injection conditions (n = 8 per group). Injections of chlordiazepoxide (0, 5.0 or 10.0 mg/kg) were given alone or in conjunction with either (+)-amphetamine (0.5 or 1.0 mg/kg) or fenfluramine (2.0 or 4.0 mg/kg). All injections were given i.p., 30 min before the feeding test, and isotonic saline served as the control injection.

By itself chlordiazepoxide did not affect the amount of food intake, compared with the control level of intake (2.2 $\pm$ 0.24 g; mean $\pm$ s.e. mean). Both (+)-amphetamine and fenfluramine, however, significantly reduced food intake ($F = 21.75$, d.f. 2,63, $P < 0.001$ and $F = 51.69$, d.f. 2,63, $P < 0.001$) respectively. The anorexic effects were matched, e.g. intakes after (+)-amphetamine (0.5 mg/kg) and fenfluramine (2.0 mg/kg) were 1.3 $\pm$ 0.18 and 1.3 $\pm$ 0.19 respectively. Chlordiazepoxide (5.0 mg/kg) effectively blocked the anorexic effect of (+)-amphetamine, reflected in the significant drug-interaction term ($F = 2.78$, d.f. 4,63, $P < 0.03$), but failed to block the effect of fenfluramine. Chlordiazepoxide reliably prolonged the duration of feeding ($F = 19.2$, d.f. 2,63, $P < 0.001$), whilst both (+)-amphetamine and fenfluramine attenuated feeding duration ($F = 15.9$, d.f. 2,63, $P < 0.001$ and $F = 29.29$ d.f. 2,63, $P < 0.001$, respectively). The effects of chlordiazepoxide and (+)-amphetamine on feeding duration were additive (i.e. a non-significant drug interaction, $F < 1.0$). However, there was a significant interaction between chlordiazepoxide and fenfluramine ($F = 5.03$, d.f. 4,63, $P < 0.002$), and the higher dose of chlordiazepoxide increased the effect of fenfluramine to shorten the eat-