# Effects of dihydroergotamine on glucose and galactose tolerance in the rabbit

Charbonnier & Cachin (1967), from experiments on the effects of dihydroergotamine (DHE) on some hepatic function tests in man, have suggested that DHE may increase the cellular metabolism of galactose since they found that the alkaloid reduced the urinary excretion of galactose in the oral galactose tolerance test. The following experiments were done to assess the effects of DHE on overall carbohydrate metabolism in rabbits.

Young adult, male rabbits, 1900–2100 g, were normally fed "Purina" standard rabbit pellets, with water *ad lib.* They were allowed no food or drinking water for 8 h before and during the experiments. Thirty min before zero time they were put into tubular restraining wire cages for the duration of the experiment. At zero time blood was taken from an ear vein for determination of fasting blood glucose concentration, an indwelling bladder catheter was inserted, and 1 ml of 0·9% NaCl solution either plain (saline controls) or containing DHE methanesulphonate (0·1 or 1·0 mg $kg^{-1}$) was given into the vein of the opposite ear. At 30 min after zero time the animals were all given water 50 ml $kg^{-1}$ by gavage (to promote gut absorption and urine flow) and, where applicable, they were loaded either intravenously or in the gavage fluid with glucose or galactose 500 mg $kg^{-1}$. For intravenous loading the sugars were injected into an ear vein as 25% (w/v) sterile, aqueous solutions. Blood was taken at 1, 2 and 4 h after zero time, always from the ear opposite to the one in which DHE had been injected. The urine was collected continuously over the 4 h of the experiments. Blood and urine sugar concentrations were determined by specific oxidase methods using Boehringer and Kabi kits for glucose and galactose respectively.

In experiments in which rabbits were not loaded with extra sugar, neither dose of DHE had any significant effect on fasting blood glucose concentrations. As shown in Table 1 however, DHE raised the 1 h peaks of blood glucose after parenteral loading and depressed these peaks after enteral loading with glucose. Urinary excretion of glucose was depressed by DHE after both parenteral and enteral glucose loading. Differences of effects between the two dosage levels of DHE were not significant. From the results shown in Table 2 essentially the same changes occured after galactose loading. DHE raised the blood galactose peak after parenteral galactose loading and depressed the peak after enteral loading. Only the higher dose of DHE showed a significant effect with parenteral galactose loading. Urinary excretion of galactose was significantly lowered by both doses of DHE after both loading routes but dose effects were not significant. No significant changes were seen in blood glucose in these galactose experiments.

The reduced urinary excretion of galactose after DHE dosing in rabbits agrees with the results of Charbonnier & Cachin (1967) in man, but the fact that this finding occurred after sugar loading by the parenteral route with blood sugar concentrations

Table 1. *Effects of DHE on blood and urinary glucose after parenteral and enteral glucose loading. Values are means ±s.e. for 5 rabbits in each treatment group.*

| Treatment | Parenteral (i.v.) loading Blood glucose (mg %) 0 h | 1 h | 2 h | 4 h | Urine (mg total) | Enteral loading Blood glucose (mg %) 0 h | 1 h | 2 h | 4 h | Urine (mg total) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 ml saline i.v. | 78 ± 4 | 141 ± 3 | 87 ± 4 | 77 ± 5 | 61 ± 5 | 80 ± 3 | 125 ± 4 | 81 ± 3 | 76 ± 2 | 20 ± 4 |
| DHE 0·1 mg $kg^{-1}$ i.v. | 80 ± 3 | 156 ± 3* | 94 ± 3 | 79 ± 3 | 34 ± 5* | 82 ± 4 | 101 ± 3* | 89 ± 2* | 78 ± 4 | 8 ± 2* |
| DHE 1·0 mg $kg^{-1}$ i.v. | 78 ± 4 | 159 ± 4* | 93 ± 5 | 80 ± 4 | 29 ± 3* | 80 ± 2 | 98 ± 3* | 87 ± 3 | 80 ± 4 | 7 ± 3* |

* Significant relative to corresponding control group ($P \leqslant 0.05$).

Table 2. *Effects of DHE on blood glucose and galactose and urinary galactose after parenteral and enteral galactose loading. Values are means ± s.e. for 5 rabbits in each experimental group. (Gluc. = glucose; Gal. = galactose). (—) = galactose undetected.*

| Galactose Loading Route | Treatment | Blood sugar (mg %) 0 h Gluc. | 1 h Gluc. | 1 h Gal. | 2 h Gluc. | 2 h Gal. | 4 h Gluc. | 4 h Gal. | Urine (mg total Gal.) |
|---|---|---|---|---|---|---|---|---|---|
| Parenteral (i.v.) | 1 ml Saline i.v. | 80 ± 3 | 98 ± 5 | 59 ± 2 | 95 ± 3 | 11 ± 4 | 76 ± 3 | (—) | 90 ± 6 |
| | DHE 0·1 mg kg$^{-1}$ i.v. | 81 ± 4 | 87 ± 4 | 64 ± 3 | 98 ± 6 | 13 ± 3 | 78 ± 4 | (—) | 62 ± 5* |
| | DHE 1·0 mg kg$^{-1}$ i.v. | 78 ± 4 | 85 ± 4 | 70 ± 2* | 89 ± 5 | 15 ± 4 | 74 ± 2 | (—) | 65 ± 8* |
| Enteral | 1 ml Saline i.v. | 79 ± 4 | 95 ± 5 | 47 ± 4 | 83 ± 6 | 20 ± 2 | 75 ± 3 | (—) | 73 ± 5 |
| | DHE 0·1 mg kg$^{-1}$ i.v. | 80 ± 2 | 85 ± 5 | 35 ± 3* | 88 ± 6 | 19 ± 4 | 77 ± 4 | (—) | 57 ± 4* |
| | DHE 1·0 mg kg$^{-1}$ i.v. | 76 ± 3 | 82 ± 5 | 31 ± 4* | 84 ± 3 | 28 ± 3 | 72 ± 2 | (—) | 58 ± 4* |

* Significant relative to corresponding control group ($P \leqslant 0{\cdot}05$).

greater than controls suggests that the effect is mainly mediated by an action on kidney function rather than by increased metabolism (cellular uptake) of sugar. It is suggested that the differences in blood sugar concentrations caused by DHE after parenteral and enteral sugar loading might be mainly ascribed to some known effects on regional blood flow which would indirectly alter the rate of handling of the sugar, particularly in the gut and kidney. It has been shown in man (Freis, Stanton & others, 1949), and I have confirmed it in rabbits, that dihydrogenated ergot alkaloids decrease the renal blood flow, and usually decrease the hepatoportal and splanchnic (enteral) blood flow rates. The relative effects of decreased gut absorption of sugar (predominating after enteral loading) and decreased urinary excretion (predominating after parenteral loading) could account for the changes seen. A direct effect by DHE on the cellular metabolism of sugars in the liver or elsewhere is not excluded but increased cellular uptake of sugars seems unlikely to be significant. Reduction of hepatoportal blood flow might be expected in fact to reduce sugar uptake by the liver, where much glucose and most galactose (Fischer & Weinland, 1965) are metabolized. Moreover, in studies on the effects of DHE on rabbit liver homogenates I have made, DHE slightly, but significantly increased glucose but not galactose release and had no effect on sugar uptake in liver cells *in vitro*. Of some clinical importance however is the possibility that glucose and galactose tolerance tests in man might be significantly altered by treatment with dihydrogenated ergot alkaloids.

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