The action of endotoxin in mobilizing free fatty acid

SIR,—Hirsch, McKay & others (1964) have reported a rapid increase of the plasma free fatty acid level in rabbits given endotoxin intravenously.

Salmonella typhi endotoxin purified according to Boivin and Mesrobeanu, was given intravenously (10^{-3} LD50 in an 0·1 ml/kg volume) to male rabbits of 2·5–3 kg weight. Blood samples were taken by cardiac puncture from the animals starved for 18–20 hr. The serum free fatty acid content was measured photometrically (Mosinger, 1965).

The normal free fatty acid content of rabbit serum was found to be 0·46 mmole/litre (s.d. $\pm$ 0·066) in an average of 11 animals. Endotoxin was administered intravenously to 9 groups of rabbits each of 6 animals and blood samples were withdrawn 1, 2, 3, 4, 8, 16, 32, 48, 64 hr after the injection. The serum free fatty acid level exhibited an initial increase (91·3%) in the first hr (Fig. 1). Up to the end of the second hr, a maximum level of 122% of the normal was obtained. By the end of the third hour, the serum free fatty acid had returned to about its original level. This was followed by a slow and moderate increase after the sixteenth hr, which returned to the normal level after 64 hr.

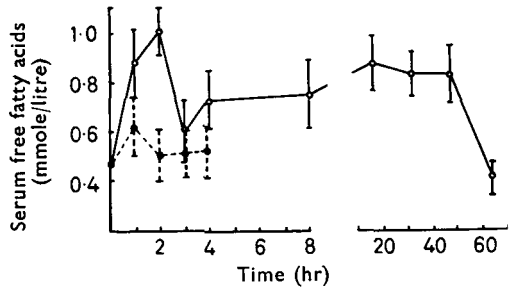

FIG. 1. Influence of *Salmonella typhi* endotoxin on the free fatty acid level of the rabbit serum. Dose: 10^{-3} LD50, 0·1 ml/kg i.v. The starting point is the average of 11, while the other points represent averages of 6 animals each.

The experiments were extended to a control group given the same volume of distilled water instead of endotoxin and in which no significant change occurred.

To examine the possible mechanism of the phenomenon, an examination of the initial response was undertaken.

The experiments were made on groups of 6 rabbits each as previously described. The free fatty acid-mobilizing effect of endotoxin was measured in groups either by transection of the spinal cord or by observing the effects of various sympathetic blocking substances.

Animals of the control groups were sham operated under hexobarbitone anaesthesia. Skin was incised above the cervical part of the vertebral column, the muscles were retracted and the spinous process removed. The wound was sutured and blood sample was withdrawn from the heart after 24 hr. The average free fatty acid level was increased to 1·01m mole/litre (Fig. 2A). This increase was identical with that observed in endotoxin-treated rabbits 2 hr after the injection. When given endotoxin 2 hr after the withdrawal of blood, these rabbits exhibited a further 60% increase of serum free fatty acid. Transection of the spinal cord resulted in a similar elevation of serum free fatty acid to that of the sham operated animals. Administration of endotoxin, to operated animals, however, failed to elicit a further increase.

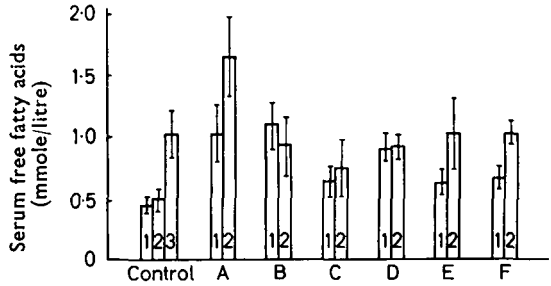

FIG. 2. Control. 1, control; 2, 120 min after 0·1 ml/kg distilled water i.v.; 3,1 20 min after endotoxin, 10^{-3} LD50 0·1 ml/kg i.v. A.1. 24 hr after sham-operation, untreated. A.2. 24 hr after sham-operation, endotoxin given 2 hr before cardiac puncture. B.1. 24 hr after spinal transection, untreated. B.2. 24 hr after spinal transection, endotoxin given 2 hr before cardiac puncture. C.1 140 min after 2 mg/kg Dibenamine i.v. C.2. 140 min after Dibenamine, endotoxin given 120 min before cardiac puncture. D.1. 140 min after 1 mg/kg yohimbine i.v. D.2. 140 min after yohimbine, endotoxin given 120 min before cardiac puncture. E.1. 140 min after 2 mg/kg pronethalol i.v. E.2. 140 min after pronethalol, endotoxin given 120 min before cardiac puncture. F.1. 140 min after 2 mg/kg Sanotensin. F.2. 140 min after Sanotensin, endotoxin given 120 min before cardiac puncture.

The effect of various drugs was studied in two groups of rabbits. Both received the same doses followed 140 min later by cardiac puncture. One of the groups was also given endotoxin 120 min before blood samples were taken.

In the first experiment, α-receptor blocking agents were tested (Fig. 2C, D). Dibenamine induced a moderate increase (0·61 mmole/litre) of serum free fatty acid. Administration of endotoxin hardly affected this value (0·72 mmole/litre). This difference was considered to be within the limits of experimental error. Yohimbine increased the free fatty acid content to 0·90 mmole/litre. Endotoxin failed to increase the free fatty acid level further.

In the next experiment (Fig. 2E), the effect of the β-receptor inhibitor pronethalol was like that of Dibenamine, in inducing a moderate elevation of serum free fatty acid. Administration of endotoxin to this group gave an average increase of 122%—similar to that of the controls; and in this pronethalol failed to inhibit the effect of endotoxin. Sanotensin (2-octahydro-1-azocinyl-ethyl-guanidine sulphate), a substance inhibiting the release of catecholamine, behaved similarly (Fig. 2F).

Our findings suggest the involvement of the central nervous system in endotoxin-induced free fatty acid mobilization.

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Department of Pathophysiology,
National Institute of Public Health,
Budapest IX, Hungary
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J. TUZSON
P. KERTAI

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