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# The Physiological Effect of Glucagon on Fat-Mobilisation

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*Summary.* In normal dogs under pentobarbital anaesthesia, intraportal infusion of physiological doses (0.002 µg/kg/min) of cystein-treated glucagon increases markedly the plasma FFA levels in the peripheral blood. This can be considered as an argument for a possible role of glucagon as a physiological regulator of lipid metabolism.

*Effet physiologique du glucagon sur la mobilisation des lipides.*

*Résumé.* La perfusion portale de doses physiologiques (0.002 µg/kg/min) de glucagon traité par la cystéine augmente de façon très significative le taux sanguin des acides gras libres du plasma périphérique. Cette observation constitue un argument en faveur d'un rôle physiologique du glucagon dans le métabolisme des lipides.

*Der physiologische Effekt von Glucagon auf die Fettmobilisation.*

*Zusammenfassung.* Die intraportale Infusion von physiologischen Dosen von Glucagon, das mit Cystein behandelt ist (0.002 µg/kg/min) erhöht bei normalen Hunden unter Pentobarbital-Anaesthesie eindeutig die Plasmaspiegel der freien Fettsäuren im peripheren Blut. Dieser Effekt kann als Hinweis auf die physiologische Bedeutung des Glucagons im Fettstoffwechsel angesehen werden.

*In vitro*, glucagon increases free fatty acid release from rat adipose tissue (Steinberg et al., 1959; Hagen, 1960; Weinges, 1961). This effect results from increased lipolysis (Weinges and Löffler, 1965) with concomitant increased reësterification as shown by Vaughan and Steinberg (1963) with their "non isotopic balance method", and by ourselves (Lefebvre, 1966).

An effect on FFA release has been detected by Weinges (1961) with concentrations of glucagon of 0.004 µg/ml and by Lefebvre (1966) with concentrations of 0.002 µg/ml, which are in the range of the physiological levels evaluated in plasma by Unger et al. (1962).

*In vivo*, the effects of glucagon on plasma FFA have led to conflicting results: a fall in plasma FFA in man was observed by Lipsett et al. (1960), Pennick and Hinkle (1960), Eymer et al. (1961) and Dreiling et al. (1962), and in dog by Steinberg et al. (1959); an early rise by Weinges (1961) in man, and by Levarlet (1962) in dog; an initial fall and a secondary rise, in man, by Felber and van Itallie (1958) and by Lipsett et al. (1960). We recently reported (Lefebvre, 1965) that, in man, glucagon at the dose of 1 mg/m², induces an initial fall of plasma FFA followed by a marked secondary rise, which can be observed between the 2nd and 5th hour after the injection. This initial fall can be reproduced by an hyperglycemia of the same magnitude as the one caused by glucagon, and induced by i.v. glucose infusion. The secondary rise is much more important after glucagon than the small rebound-effect observed after glucose. This secondary rise could correspond to the fat-mobilizing effect of the hormone.

Nevertheless the physiological signification of these experiments has not been established. In the experiments reported here, we studied the effects on plasma FFA of physiological doses of glucagon perfused in the physiological site of secretion of the hormone i.e. the portal vein.

## *Material and Methods*

A short laparotomy was performed in 10 normal mongrel dogs, under sodium pentobarbital anaesthesia. The animals were fasted for 18 hours before the experiment. The body temperature was kept constant by warming blankets. A catheter *(Clay Adams P.E. 240)* was introduced into the portal vein through the splenic vein. Blood samples were collected from the femoral vein. During the 5 hours of the experiment, 9 ml/hour of normal saline was infused into the portal vein. In 6 out of the 10 animals, a solution of glucagon was substituted for the saline for one hour (cystein-treated glucagon (Novo) in saline at the concentration necessary to give an infusion of 0.002 µg/kg body weight per minute).

Blood glucose was determined according to Hoffman's method (1937) adapted to the *Technicon Auto-Analyser*. FFA were determined by the method of Dole (1956) modified in our laboratory (Lefebvre and Henrioul, 1963).

## *Results*

Table 1 shows the values of blood glucose and plasma FFA in both the glucagon infused and the control dogs. In the limits of the periods of time studied, we did not observe any difference in blood glucose between the two groups. As regards plasma FFA, the values are significantly higher between the 60th and the 240th minutes in the glucagon-treated animals (Fig. 1). The differences are statistically, highly significant ($p < 0.05$).

Table 1. *Blood glucose and plasma FFA in control and intraportally glucagon-infused dogs*

| | | Initial values = 100% | % of initial values (mean of 3 determinations before starting the experiment) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 30 min | 60 min | 90 min | 120 min | 180 min | 240 min | 300 min |
| Blood glucose | Control | 76[1] ± 2.6[2] mg % | 97 ± 3.1 | 105 ± 3.1 | 94 ± 3.1 | 96 ± 3.1 | 89 ± 3.1 | 89 ± 4.3 | 87 ± 7.6 |
| | Glucagon 0.002 µg/kg/min intraportal[3] | 77.8 ± 4.4 mg % | 101 ± 4.1 | 93 ± 3.2 | 86 ± 2.2 | 82 ± 3.6 | 82 ± 3.9 | 83 ± 6.3 | 86 ± 7.3 |
| | p | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. | N.S. |
| Plasma FFA | Control | 634 ± 24 µEq ‰ | 84 ± 8.7 | 79 ± 14.1 | 81 ± 8.9 | 90 ± 7.6 | 95 ± 7.6 | 104 ± 10.2 | 110 ± 12.5 |
| | Glucagon 0.002 µg/kg/min intraportal[3] | 575 ± 24 µEq ‰ | 116 ± 11.1 | 131 ± 11.4 | 148 ± 10.9 | 156 ± 12.2 | 150 ± 9.4 | 146 ± 8.1 | 148 ± 9.4 |
| | p | N.S. | N.S. | < 0.05 | < 0.01 | < 0.01 | < 0.01 | < 0.02 | N.S. |

[1] mean.
[2] standard error of the mean.
[3] during the first hour.
n of experiments is 4 in controls and 6 in glucagon infused animals.
N.S. Not statistically significant.

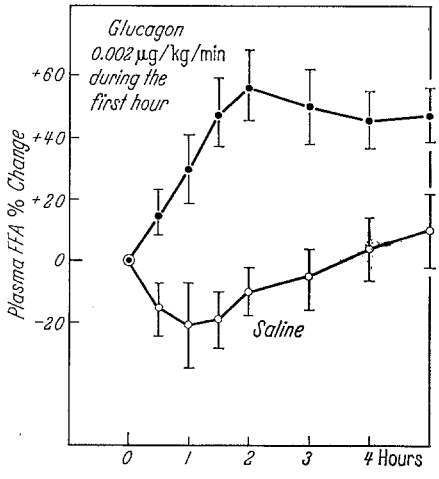


Fig. 1. Changes in plasma FFA during and after intraportal infusion of glucagon. Comparison with saline-infused dogs. Mean of 6 (glucagon-treated) and 4 (controls) animals ± S.E.M.

## *Discussion*

The dose of 0.002 µg/kg/min of glucagon infused into the portal vein can be considered as physiological in respect of: (1) the levels of the "glucagonemia" found by UNGER et al. (1962) in the pancreatic venous plasma of chronically hypoglycemic dogs: 680–3100 µµg Eq/ml (mean value 1976 µµg Eq/ml) and (2) the values of the pancreatic venous blood flow in the dog, which are in the range of 2 ml of blood, approximatively 1 ml of plasma per kg per min (LOUBATIÈRES, personal communication).

We have demonstrated that such physiological doses are able to increase the plasma FFA level in peripheral blood. This can be considered as an argument for a possible role of glucagon as a regulator of lipid metabolism.

The lack of hyperglycemic response in our experiments could be explained by: (1) the sensitivity of the hyperglycemic response, which is about 0.1 µg/kg (STAUB and BEHRENS, 1954), the total dose given here in 1 hour being 1.2 µg/kg and (2) the fact that we have only studied peripheral blood samples where minimal changes could not be detected but might appear in subhepatic venous blood.

These experiments suggest that the FFA-mobilizing effect of glucagon could be of importance under the physiological conditions that increase its portal concentration, such as fasting or hypoglycemia (UNGER et al., 1962; UNGER and EISENTRAUT, 1965).

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