Free Fatty Acid-Glucagon Feed-Back Mechanism

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Summary. In order to study the existence of a free fatty acid-glucagon feed-back mechanism *in vivo*, adult male Peking ducks were infused with 2 physiological fatty acids: oleic and linoleic acids. The animals received IV infusions of 0.365 g FFA/kg/30 min as an emulsion in their own plasma drawn a few weeks earlier. After 5 min of infusion a significant fall of the circulating GLI level occurred; it dropped to 50% of the pre-infusion value after 30 min infusion. Simultaneously slight hypoglycemia developed. The nature of the GLI involved was established by repeating these experiments

with totally pancreatectomized animals (only gut GLI) and partially eviscerated ones (only pancreatic IRG); in the last group the basal level of circulating FFA was slightly reduced. These experiments showed that the pancreatic IRG was involved in this feed-back mechanism which might be non-insulin-dependent. In addition, an intestinal factor could be involved in fasting FFA mobilization.

Key words: Duck, feed-back mechanism, glucagon, FFA, fasting, intestinal lipolytic factor.

The relationship between pancreatic glucagon (IRG) and plasma free fatty acids (FFA) has already been studied by several workers.

Intraportal infusions of physiological concentrations of glucagon provoke a delayed rise in peripheral FFA in dogs and man [27]. An earlier rise in plasma FFA in response to a glucagon infusion can only be realised if the insulinogenic effect of glucagon is reduced by starving the dogs for three days [36].

Conversely, the infusion of triglycerides and heparin, which produces an increase in circulating FFA, induces a decrease in peripheral glucagon immunoreactivity (GLI) in dogs [28]; this GLI is known to be of pancreatic origin as peripheral plasma variations parallel changes in the pancreaticoduodenal vein concentration [38].

A negative feed-back relationship between glucagon and FFA would seem to be present in mammals; but there is no proof that this is either a rapid or a sensitive interplay.

In birds, the situation is somewhat different. Several authors have pointed out the unequivocal lipolytic effect of glucagon and the extreme sensitivity of avian adipose tissue to this hormone: in chickens [10, 14, 21], in owls [13], and in ducks [10, 7]. Its remarkably high activity would seem to be because insulin is devoid of an antilipolytic effect in birds [11, 5]; the insulin secretion induced by glucagon does not interfere with the lipolytic effect of glucagon in this species. The duck therefore appeared particularly appropriate for studies on a glucagon-FFA feed-back mechanism. Another reason which prompted us to use it as an experimental animal was that total pancreatectomy is followed by a drop in plasma FFA [6].

In the present paper we wish to demonstrate the existence of a glucagon-FFA feed-back mechanism in

physiological conditions. To do this, we studied the effect of an infusion of oleic or linoleic acid on plasma levels of pancreatic and gut glucagon. The amounts of fatty acids were those calculated to mimic the normal doubling of FFA concentration which accompanies an overnight fast. We also examined the functioning of such a feed-back mechanism in diabetic animals. This was considered important in the light of other results implying an impairment of the glucagon-glucose feed-back mechanism during diabetes in man and dog [40, 35], and the goose and duck [18].

Material and Methods

I. Animals

The 90 adult male Peking ducks used were maintained on a normal fowl diet (Fortis Dusquesne) and tap water. They weighed between 1.6 and 2.5 kg. Before the experiments they were transferred indoors, installed in individual cages, and fasted for 16–20 h.

II. Operations

1. **Total and Subtotal Pancreatectomies.** The operations were performed according to the technique detailed by Mialhe [32]. In the subtotally depancreatized ducks the anterior part of the splenic lobe (representing 1 to 2% of the pancreas) is left.

2. **Partial Evisceration.** The duodenum of the duck, unlike that of mammalian species, is devoid of GLI activity [19]; this means that it can be retained without prejudicing plasma GLI levels. Partial eviscerations, in which the pancreas and duodenum are left attached, were performed according to the procedure of Krug and al. [20]: the plasma GLI is then of pancreatic origin.

only the first metabolite requires the presence of insulin. This conclusion may not be valid in mammals as the high levels of FFA observed in diabetes [2, 3, 24] would be expected to reduce glucagon secretion; apparently however, they do not [2, 40, 35].

III. Relative Importance of the Glucose-Glucagon and FFA-Glucagon Feed-Back Mechanisms

Studies on this problem have so far yielded contradictory results. Data obtained [8] with isolated guinea pig islets suggested that FFA were stronger inhibitors of glucagon secretion than glucose. With an isolated perfused rat pancreas preparation, FFA were concluded to have an important, but not predominant, role in the regulation of glucagon output [29]. The slight decrease of the plasma glucose level observed during the course of the oleic acid infusion in normal and partially eviscerated ducks, may reduce the effects of the increased FFA level. Indeed, an important decrease of plasma GLI or pancreatic glucagon is noted during the first ten minutes of infusion; no further decrease is observed unless the concentration of FFA in the perfusate is subsequently increased; in that situation, the secondary hypersecretion of glucagon is suppressed, probably by the high level of FFA.

We know that the glucose-glucagon feed back mechanism is extremely sensitive in a species very similar to the duck, the goose [39]; a variation of the basal glucose level of 5% is enough to bring about a change in the plasma glucagon level. In our experiments on partially eviscerated ducks, a significant decrease of plasma pancreatic IRG is induced by increasing the basal FFA by 190%: the FFA-glucagon feed-back mechanism therefore seems to be less sensitive than the glucose-glucagon one. However observations on starved ducks [36, 7] show no change in plasma GLI when plasma FFA are doubled, and plasma glucose reduced by 10%. We are therefore unable to assess the relative importance of the two feed-back mechanisms in the duck.

IV. Regulation of FFA Level in the Duck

After total pancreatectomy, the blood glucose level decreases very rapidly, but the FFA level is normal at the time of the infusion. A factor other than pancreatic glucagon, must be responsible for the maintenance of FFA levels. This is also suggested by the fact that there is a decrease in the plasma FFA level after partial evisceration yet the plasma pancreatic IRG remains within the normal range. These observations are in accordance with the postulated existence of intestinal lipolytic factors [21].

Conclusion

A free-fatty acid-pancreatic glucagon feed-back mechanism working in physiological conditions has been demonstrated in the duck; it might be non-in-

sulin dependent. Gut GLI is not involved in this regulation.

Pancreatic glucagon does not seem to be the only factor responsible for the maintenance of FFA level in fasting ducks.

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