Diss. ETH 5377

STUDIES OF CARBOHYDRATE, FAT AND AMINO ACID METABOLISM IN VIVO AND IN ISOLATED SKELETAL MUSCLE OF LEAN AND OBESE – HYPERGLYCEMIC (C57 B1 6j -ob/ob) MICE

ABHANDLUNG

zur Erlangung

des Titels eines Doktors der Naturwissenschaften

der

EIDGENÖSSISCHEN TECHNISCHEN

HOCHSCHULE ZÜRICH

vorgelegt von

GUY CUENDET

Dipl. Naturwissenschaften, ETH Zürich

geboren am 12. April 1949

von Ste-Croix (Kt. Vaud)

Angenommen auf Antrag von

Prof. Dr. G. Semenza, Referent

Prof. Dr. A. E. Renold, Korreferent

aku-Fotodruck

Zürich

1974

VIII Summary

The present work has made contributions in three areas, all related to the interplay of substrates and hormones.

1) A relationship has been shown between the plasma levels of fat-derived substrates, free fatty acids, B-hydroxybutyrate and acetoacetate, on the one hand, and nitrogen "sparing", on the other hand. The latter was manifested by progressive decline of the daily urinary losses of urea nitrogen. This relationship was seen in fasted obese and both fasted and fat-fed lean mice, suggesting that the availability of increased adipose stores was the principal cause of the nitrogen "sparing" capability of obob mice.

2) Incubation studies of soleus muscle demonstrated that the so-called "glucose-fatty acid cycle" of Randle is operative in isolated skeletal muscle obtained from lean mice, since addition of fat-derived substrates inhibited the uptake and oxidation of glucose.

3) Evidence has been obtained that glucose uptake of skeletal muscle from obese (C57 Bl 6j -ob/ob) mice is diminished both in the basal state and during stimulation by insulin. The data with 2-deoxy-glucose favour transport as the site of the defect, but they do not suffice to definitively establish this interpretation. Decreased uptake in the basal state was especially striking and was not altered by metabolic manipulations, which did increase insulin response. Accordingly it is suggested that decreased glucose transport and/or phosphorylation may be the primary lesion in muscle of obob mice, resistance to insulin action being secondary, at least in part. Defective glucose uptake by muscle might provide a rational explanation for, or at least be a contributing factor to the development of the obese-hyperglycemic syndrome.