Regulation of Human Lipolysis

IN VIVO OBSERVATIONS ON THE ROLE OF ADRENERGIC RECEPTORS

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ABSTRACT Changes in the plasma free fatty acids of a pancreatectomized subject and in free fatty acids and insulin in 10 normal subjects in response to the in vivo infusion of epinephrine alone, epinephrine plus phentolamine, and epinephrine plus propranolol indicate that both alpha and beta adrenergic receptors are present in human adipose tissue. Under the experimental conditions used, adipose tissue appeared to be more responsive to epinephrine than did the cardiovascular system.

INTRODUCTION

It has been postulated that adrenergic receptors are linked to the adenylyl cyclase-cyclic AMP system (1). According to this hypothesis an effective interaction of a catecholamine with beta adrenergic receptors causes activation of adenylyl cyclase, an increase in cyclic AMP, and an increase in hormone response, while interaction with alpha sites reduces the effective concentration of cyclic AMP leading to an opposite effect on cell function. We have recently tested this hypothesis with a homogenous cell system consisting of human adipocytes, and our findings agreed closely with those predicted by the hypothesis (2, 3). Obviously, the significance of these observations would be enhanced if similar findings were made in the intact human. The in vivo demonstration of alpha site activity in adipose tissue is complicated by the fact that adrenergic agonists and blockers have widespread effects. Particularly troublesome is the influence of catecholamines on the secretion of insulin, a potent antilipolytic hormone. The effects of catecholamines on the cardiovascular system might also obscure or distort metabolic responses. In an attempt to circumvent or minimize these problems, two approaches were used as described below.

METHODS

Experimental design I. The first approach (see Fig. 1) depended on the absence of regulated insulin secretion. A 20-yr-old man who had undergone a total pancreatectomy a year earlier for an islet cell adenoma located immediately adjacent to the duodenum was studied over an 8-day period. The subject's acquired diabetes was reasonably well controlled and other than an occasional loose stool, he had no complaints and appeared to be in good health. On days 2 and 6, propranolol was administered; on day 4 and 8, phentolamine was given; no experiments were done on days 1, 3, 5, and 7. On each experimental day, the patient fasted, and his insulin was withheld until after the study was completed. Each study consisted of four 60-min periods. Initially, saline was infused (period I). This was followed by either propranolol, 0.08 mg/min or by phentolamine, 0.5 mg/min (periods II and III); finally epinephrine was infused at a rate of 6 μg/min (periods III and IV). The blockers and epinephrine were obtained from commercial sources; the doses used had been administered without difficulty by Porte (4). Blood was obtained every 15 min for estimation of plasma free fatty acids (5) and glucose. Glucose determinations were made with a prepared reagent, Glucostat obtained from the Worthington Biochemical Corp., Freehold, N. J. Vital signs were closely monitored.

Experimental design II. The rationale of the second experimental design (see Fig. 2) was based in part on the possibility that adipose tissue may be more sensitive to epinephrine than other responsive tissues, such as the islet cells of the pancreas or the cardiovascular system. Accordingly, graded doses of epinephrine were infused into 10 normal fasting young adults. Each subject was studied on 3 different days. Each study was comprised of five 45-min periods. Saline was infused during period I; either propranolol (0.08 mg/min) or phentolamine (0.5 mg/min)
was then commenced and infused at a constant rate through periods II, III, IV, and V. In a third series of experiments, saline was continued through period II and no blocker was administered. Epinephrine was started at the onset of period III at a rate of 0.25 µg/min. This was increased to 0.5 µg/min at the beginning of period IV, and then to 1 µg/min (period V). Blood pressure and pulse were determined every 15 min, and blood was obtained for the estimation of free fatty acids, glycerol (6), glucose, and insulin (7).

All subjects studied were hospitalized on the ward of the Clinical Research Center. The protocols followed were approved by the institution’s Committee for Projects Involving Human Subjects. The study was explained to each subject and written consent obtained.

Statistical analysis. Standard errors of means were calculated to express the scatter of the data but were not used for comparison purposes. The control values (period I) of the various parameters studied were compared with the values obtained during periods III, IV, and V with the sign test (8).

RESULTS

Experimental design I. During the infusion of saline, propranolol, phentolamine, and the combination of propranolol and epinephrine (period III) the subject was free of symptoms. However, during the administration of epinephrine and phentolamine, the patient was anxious and developed palpitation and mild muscular twitching. Midway during the second phentolamine experiment, the patient complained of chest discomfort and the study was terminated. Except for change in rate, continuous monitoring of the electrocardiograph revealed no changes during any of the four studies.

FFA results expressed as a percent change from the mean of control values are contained in Fig. 1. Each point represents the mean of FFA values obtained on two different days. Propranolol alone depressed the level of FFA in the plasma, and the addition of epinephrine exaggerated this effect, the nadir being less than 50% of baseline values. Phentolamine alone caused a slight increase in FFA and the addition of epinephrine markedly enhanced this effect to a maximum of 250% of the baseline. During the administration of either blocker, plasma glucose concentration gradually rose (data not shown).

Experimental design II. The infusion of epinephrine alone, of either blocker alone, or of the combination of epinephrine and propranolol to the group of normal subjects failed to elicit symptoms. During the administration of the higher doses of epinephrine (0.5 and 1.0 µg/min) in combination with phentolamine, several subjects complained of palpitation, anxiety, nasal stuffiness, and muscle tremor. These symptoms were very mild and in no instance was it necessary to terminate a study. As
with the pancreatectomized subject, there were no
electrocardiographic changes other than alterations in rate.

Changes in plasma FFA, glycerol, insulin, and dia-
stolic blood pressure are plotted in Fig. 2. The results
were calculated as a percent of mean control values in
each study; that is, for each subject the average of three
samples obtained during saline infusion was considered
to be 100%. In Fig. 2, each point is the mean of values
taken from each of the 10 subjects. Infusion of phentola-
mine alone during period II caused an elevation in plasma
FFA to about 130% of baseline. When epinephrine was
added during periods III, IV, and V, there was a pro-
gressive further elevation in FFA to 200%. Epinephrine
alone caused a parallel, but much less marked increase
in FFA. Propranolol alone depressed FFA, and the ad-
dition of epinephrine did not enhance this effect. Alter-
ations in the concentrations of plasma glycerol closely
paralleled that of FFA.

These results should be considered in light of the
changes in insulin concentration. The infusion of epi-
nephrine plus phentolamine was associated with a
modest increase in insulin concentration; this increase
was statistically significant (period I vs. IV and V, P
values less than 0.05 and 0.01, respectively). The ad-
ministration of epinephrine plus propranolol caused a
slight fall in the level of insulin. Thus, the marked in-
crease in FFA seen with epinephrine plus phentolamine
occurred in spite of an augmented level of insulin, and
the depression of FFA seen with epinephrine plus pro-
pranolol occurred in the face of insulin concentrations
below the control base line.

In the presence of propranolol, the lowest infusion rate
of epinephrine caused a modest increase in diastolic
blood pressure; during the highest infusion rate this
increase was statistically significant (period I vs. V,
P < 0.01). In the presence of phentolamine, epinephrine
prompted a small but significant decline in blood pres-
sure (period I vs. III, P < 0.01). The latter effect be-
came more marked with higher doses of epinephrine.
Changes comparable in degree but opposite in direction
were noted in the pulse. Thus, while the lowest infusion
rate of epinephrine used in these experiments. 0.25
mg/min, was sufficient, in the face of adrenergic block-
ade, to alter diastolic blood pressure and pulse, these
changes were relatively small compared to those noted
in FFA concentration.

The plasma glucose concentration remained unchanged
throughout the infusion of the epinephrine-plus-phentola-
mine combination; during the infusion of epinephrine
alone and of epinephrine plus propranolol, it gradually
rose. The glucose concentrations in period V were sta-
tistically significantly higher than those of period I. The
P values for epinephrine alone and for epinephrine plus
propranolol were each < 0.01 (data not shown).

**DISCUSSION**

The results obtained with both experimental design I
and II suggest that both alpha and beta adrenergic re-
ceptor sites are present in human adipose tissue. When
alpha sites are blocked, as during phentolamine admini-
stration, the stimulation of beta sites by endogenous
catecholamines is unopposed and the level of plasma FFA
increases. This effect is substantially enhanced by the
administration of epinephrine. When beta sites are
blocked, as during propranolol infusion, lipolysis declines
and the plasma concentration of FFA tends to fall be-
low the control level. In the pancreatectomized subject
this fall was accentuated by the infusion of epinephrine,
suggesting that negative alpha sites were being stimu-
lated (experimental design I, Fig. 1). The fact that this
accentuation was not observed in normal subjects (ex-
perimental design II, Fig. 2) is unexplained.

Other interpretations are, of course, possible. The in-
crease in plasma FFA concentration seen during phentol-
amine administration conceivably could have been
secondary to its effects on muscle. Thus, if the calori-
genic action of epinephrine was blocked by phentola-
mine, presumably the rate of oxidation of FFA in muscle
would decline, resulting in a rise in plasma FFA con-
centration, even though the rate of lipolysis had remained
unchanged. Hemodynamic changes might have modified
blood flow in adipose tissue resulting in an alteration in
the rate of delivery of FFA to the general circulation;
conceivably hemodynamic changes might have influ-
enced the disposal rate of released FFA. However, in view of
the close parallelism between the in vitro results previ-
ously reported and the findings reported here, it would
seem unlikely that circulatory changes alone could ac-
count for the present data.

Dual adrenergic receptors appear to be operative in
other metabolically important tissue. Turtle and Kipnis
(9) demonstrated the presence of both alpha and beta
receptors in rat pancreatic tissue, and Batzri, Selinger,
and Schramm (10) have presented evidence indicating the
existence of both alpha and beta sites in rat parotid
gland tissue; the former prompted release of potassium
ion while the latter stimulated amylase secretion. Pro-
pranolol had no effect on the alpha adrenergic response,
suggesting that the alpha receptor response in this tissue
is not related to cyclic AMP.

If we assume that both beta and alpha adrenergic re-
ceptors are present in human adipose tissue, basic ques-
tions remain unanswered. Does alpha site stimulation
reduce cyclic AMP by inhibiting adenylate cyclase by
stimulating phosphodiesterase, or by some other mecha-
nism? More fundamental questions concern the survival
value that dual adrenergic sites had primitive man, and
the physiological advantage, if any, of such a system to
modern man. Of interest are the recent studies of Rosen-
quist (11) demonstrating that adipose tissue from hypo-
thyroid patients fails to respond to the lipolytic action of epinephrine; this effect was not due to impaired beta site activity, but rather to enhanced alpha adrenergic responsiveness.

Of several other species (rat, swine, dogs, rhesus monkey, guinea pig, and hamster) whose adipose tissue we have tested for alpha site activity, only two, the hamster and monkey, were found to have both beta and alpha receptors.

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REFERENCES


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