Effects of Epinephrine and Insulin on Phosphopeptide Metabolism in Adipocytes*

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Isolated adipocytes, incubated in the presence of extracellular $^{32}P$, to steady state $^{32}P$ incorporation into cellular phosphopeptides, were exposed to hormones for 5 min. Epinephrine ($10^{-6} M$) stimulated $^{32}P$ incorporation into at least 12 major phosphopeptides, distributed in the cytoplasm, endoplasmic reticulum, and plasma membrane. Quantitatively pre-eminent among these were peptides of molecular weight 123,000 and 69,000, each located both in the cytoplasm and endoplasmic reticulum. The effect of epinephrine ($10^{-6} M$) on $^{32}P$ incorporation into these two peptides was augmented by theophylline ($10^{-5} M$) in a synergistic fashion. Norepinephrine, dibutyryl cyclic AMP, adrenocorticotropic hormone (ACTH) (synthetic 1 to 24 fragment), and glucagon mimicked the effect of epinephrine.

Insulin modified adipocyte peptide phosphorylation in two ways. When present as the sole hormone, insulin (100 microunits/ml) consistently and selectively stimulated the $^{32}P$ incorporation into a peptide of molecular weight 123,000 (endoplasmic reticulum, cytoplasm) without significant alteration in the $^{32}P$ content of any other major peptide. A second effect of insulin was evident when epinephrine ($10^{-6} M$) was present simultaneously. Insulin significantly inhibited the epinephrine-stimulated phosphorylation of the molecular weight 69,000 (endoplasmic reticulum, cytoplasm) and 26,000 (plasma membrane) peptides. Nevertheless, persistence of insulin-stimulated phosphorylation of the 123,000 peptide in the presence of epinephrine was shown by a $^{32}P$ content of this peptide that was greater in the presence of both hormones than with either individually.

These findings indicate that in intact adipocytes: (a) epinephrine acutely alters the phosphorylation of a large number of adipocyte peptides, partly at least, via activation of adenosine 3':5'-monophosphate (cyclic AMP)-dependent protein kinase; (b) insulin opposes several epinephrine-stimulated phosphorylations in a manner consistent with its ability to lower epinephrine-stimulated intracellular cyclic AMP accumulation in adipocytes; and (c) insulin, in addition, exerts a unique stimulatory effect on adipocyte peptide phosphorylation that is independent of its effects on cyclic AMP metabolism and may be mediated by the generation of an as yet undefined intracellular "messenger" unique to insulin.

In an accompanying report (1) we described the major phosphopeptides generated by isolated, intact adipocytes incubated with $^{32}P$, and catalogued them by molecular weight and subcellular distribution. Steady-state $^{32}P$ incorporation into adipocyte phosphopeptides was achieved by a 2-hour incubation under the conditions described. This report will describe the perturbations of $^{32}P$ labeling of phosphopeptides from the steady state by brief exposure of $^{32}P$-labeled adipocytes to insulin, as well as to agents known to increase intracellular cyclic AMP.

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**MATERIALS AND METHODS**

Isolated fat cells were prepared and incubated in Krebs-Ringer bicarbonate containing NaH$_2$PO$_4$, for 2 hours, as described previously (1). At 2 hours, aliquots of fat cells plus medium were distributed into plastic bottles containing either the hormone or other agent or no addition. After 5 min of further incubation, the cell suspensions were centrifuged for 30 s, the infranatant medium was removed and discarded, and the cells were washed twice in sucrose, 0.25 M, Tris-Cl, 0.01 M, pH 7.4, and EDTA, 0.001 M (Medium I) at room temperature. These two washings required approximately 4 min. The cells were immediately resuspended in ice-cold Medium I and disrupted by homogenization. A sample of homogenate was saved, and subcellular fractionation was carried out as previously described (1), which required 3 to 4 hours, with maintenance of the fractions at 0-4° throughout. Homogenization of the adipocytes under these conditions com-
pletely inhibited protein kinase and protein phosphatase activity. Thus, the addition of micromolar concentrations of \( [\gamma^32P]ATP \) (10 to 20 Ci/mmol) to such a homogenate yielded no \(^3P\) transfer onto endogenous protein unless Mg\(^{2+}\) was added in excess of the EDTA present and the mixture was warmed. With respect to protein phosphatase activity, homogenates prepared from \(^3P\)-labeled intact adipocytes (exposed to epinephrine before disruption) showed no loss of \(^3P\) from any of the nine major homogenate phosphopeptides during a 4-hour incubation at 0\(^\circ\). At 23\(^\circ\) up to 30% loss of \(^3P\) from certain species was observed.

Aliquots of the \(^3P\)-labeled cellular fractions were subjected to polyacrylamide gel electrophoresis in 1% sodium dodecyl sulfate and were matched for protein content (usually 50 \(\mu\)g/gel), as determined by Lowry et al. (4), as well as for loading volume. After destaining, measurement of \(^3P\)-labeled phosphopeptides was carried out by analysis of radioautographs of dried longitudinal gel slices. Thus, in each experiment, for a given cellular fraction (e.g. homogenate, plasma membrane, etc.), the dried gel slices for the control and each experimental condition were mounted together and exposed simultaneously to a single x-ray film. The developed radioautograph was scanned densitometrically. The effect of an experimental condition on the \(^3P\) content of any single phosphopeptide was determined by the formula (A experimental/A control) minus 1 x 100 and expressed as "per cent change from control." The \(^3P\)-labeled phosphopeptides evaluated were those that were reliably and consistently identifiable in radioautographs and scans (1). An exception was the 69,000 species in the homogenate, cytoplasm, and endoplasmic reticulum, always a minor component in the presence of epinephrine, it was often a minor and poorly resolved component in scans of the control and insulin-treated fractions. The data from replicate experiments were evaluated statistically by Student's \( t \) test modified for paired data.

Glucagon-free, crystalline porcine insulin was a gift from Eli Lilly Inc. Epinephrine and norepinephrine were obtained from Parke-Davis, Inc. Epinephrine and norepinephrine-treated cells were matched for protein content and subcombined data from all experiments were evaluated statistically by Student's \( t \) test modified for paired data. Results

When fat cells labeled in the presence of \( \text{NaH}^{32}\text{PO}_4 \) for 2 hours were exposed to epinephrine for an additional 5 min, a large number of phosphopeptides exhibited significantly enhanced incorporation of \(^3P\) (Table I). Phosphopeptides of molecular weight 123,000 and 69,000 exhibited the greatest increase in \(^3P\) content. These were distributed in the cytosol and endoplasmic reticulum. In addition, at least seven other phosphopeptides in the homogenate showed significantly enhanced phosphorylation; phosphopeptides with electrophoretic mobility essentially identical with the species observed in the homogenate were detected in one or more subcellular fractions, and these also exhibited enhanced \(^3P\) incorporation in response to epinephrine (Table I). These include over one-half of the major phosphopeptides in the endoplasmic reticulum and cytosol, as well as a major plasma membrane phosphopeptide of molecular weight 26,000. The \(^3P\) content of the major phosphopeptides of the mitochondria was not significantly altered. (Amounts of nuclei recovered in these experiments were inadequate to allow systematic analysis of this fraction.) The magnitude of the increase in phosphorylation was dependent on the dose of epinephrine and was clearly evident at \(10^{-6} \text{ M} \) (Table I). In the presence of submaximal concentrations of both epinephrine (\(10^{-7} \text{ M} \)) and theophylline (\(10^{-2} \text{ M} \)), the increase in phosphorylation of 69,000- and 123,000-dalton peptides was greater than the sum of the increments due to either agent alone (Table II). Exposure of adipocytes to norepinephrine-treated cells, corresponding peaks in the A of densitometric scans of radioautographs were compared as described under "Materials and Methods" to determine the per cent change in \(^3P\) content from control due to epinephrine. The peaks are indicated by molecular weight \(\times 10^{-3}\). The number of individual experiments yielding such paired comparisons is indicated in parentheses for each fraction. The combined data from all experiments were evaluated statistically by Student's \( t \) test modified for paired data and expressed as the per cent change in \(^3P\) content from control \(\pm\) S.E. of the difference.

### Table I

#### Effect of epinephrine on peptide phosphorylation

| Peptide molecular weight | Homogenate (n = 14) | Cytosol (n = 14) | Endoplasmic reticulum (n = 14) | Plasma membrane (n = 10) | Mitochondria (n = 6) |
|--------------------------|---------------------|-----------------|-------------------------------|-------------------------|---------------------|
| 216                      | 23.9 ± 6.9\*        | 22.5 ± 7.2\*    | 29.5 ± 5.2\*                 | -5.1 ± 3.9              | 0.3 ± 6.2           |
| 123                      | 33.6 ± 5.4\*        | 30.3 ± 5.0\*    | 17.9 ± 5.5\*                 | 12.7 ± 4.3\*            | -9.5 ± 4.9          |
| 94                       | 25.2 ± 4.3\*        | 12.7 ± 4.3\*    | 25.2 ± 4.3\*                 | 12.7 ± 4.6\*            | 3.5 ± 4.7           |
| 50                       | 69.0 ± 6.5\*        | 65.3 ± 7.7\*    | 60.1 ± 7.8\*                 | 61.8 ± 7.8\*            | 15.1 ± 4.0\*        |
| 62                       | 27.6 ± 5.0\*        | 14.0 ± 4.1\*    | 25.6 ± 5.0\*                 | 15.1 ± 4.0\*            | 4.2 ± 4.5           |
| 46                       | 23.1 ± 4.9\*        | 16.6 ± 4.3\*    | 23.1 ± 4.9\*                 | 16.6 ± 4.3\*            | 14.3 ± 4.8\*        |
| 41                       | 12.6 ± 4.7\*        | -0.3 ± 4.1      | 12.6 ± 4.7\*                 | -0.3 ± 4.1              | 12.6 ± 4.7\*        |
| 34                       | 33.9 ± 6.8\*        | 14.3 ± 4.8\*    | 33.9 ± 6.8\*                 | 14.3 ± 4.8\*            | 14.3 ± 4.8\*        |
| 29                       | -5.6 ± 3.2           | 14.3 ± 4.8\*    | -5.6 ± 3.2                   | 14.3 ± 4.8\*            | 14.3 ± 4.8\*        |
| 17                       | -1.0 ± 5.0           | 14.3 ± 4.8\*    | -1.0 ± 5.0                   | 14.3 ± 4.8\*            | 14.3 ± 4.8\*        |

\* \( p < 0.01 \)

\* \( p < 0.001 \)

\* \( p < 0.02 \)
Hormonal Effects on Adipocyte Peptide Phosphorylation

... ACTH (synthetic 1 to 24 fragment), dibutyryl cyclic AMP (Fig. 1), or glucagon (data not shown) enhanced phosphorylation of the 123,000- and 69,000-dalton peptides. Finally, if adipocyte cytosol proteins, prepared from cells not prelabeled in the presence of NaH₂¹⁷PO₄, were supplemented with magnesium plus [γ⁻³²P]ATP, the addition of cyclic AMP stimulated the phosphorylation of a large number of endogenous peptides, among which were peptides of molecular weight 123,000 and 69,000 (Fig. 2).

The effects of insulin on peptide phosphorylation were distinctly different from those of epinephrine and related substances. Exposure of ³²P-labeled fat cells to insulin resulted in a consistent increase in the incorporation of ³²P into a major phosphopeptide of molecular weight 123,000 located in the cytosol and endoplasmic reticulum, whereas no other phosphopeptide in any fraction exhibited a significant change in ³²P content (Table III).

### Table II

**Effect of epinephrine and theophylline on peptide phosphorylation**

| Homogenate peptide (molecular weight) | Percent change in ³²P content due to | Epinephrine | Theophylline | Both agents |
|--------------------------------------|-------------------------------------|------------|-------------|------------|
|                                      | 0.1 µM | 1 mM | | | |
| 123,000                              | +24.3 ± 8.4* | +19.2 ± 9.0 | +68.5 ± 13.4* | |
| 69,000                               | +51.3 ± 12.7* | +45.2 ± 13.7* | +125.3 ± 20.4* | |

*p < 0.05.

**Fig. 1.** Effects of norepinephrine, ACTH, and dibutyryl cyclic AMP on adipocyte peptide phosphorylation. Adipocytes incubated for 2 hours at 37°C with NaH₂¹⁷PO₄ were divided into four aliquots and exposed for an additional 5 min either to norepinephrine (1 µM), synthetic 1 to 24 fragment of ACTH (0.1 µM), dibutyryl cyclic AMP (DBCA) (5 mM), or to no addition (control). The cells were then washed, homogenized, and processed as described under “Materials and Methods” and Table 1. Shown is the reversed image of the radioautograph derived from dried gel slices containing ³²P-labeled homogenate (H), cytosol (S), and endoplasmic reticulum (ER) fractions obtained from the four samples of adipocytes. TD, tracking dye.

**Fig. 2.** Cyclic AMP-stimulated phosphorylation of endogenous cytoplasmic peptides. Adipocytes were prepared, homogenized without incubation with NaH₂¹⁷PO₄, and a cytosolic fraction was obtained. Cytosol (125 µg of protein) was incubated in a volume of 200 µl with 0.2 M sucrose, 10 mM Tris-Cl, pH 7.4, and 10 mM MgSO₄. The reaction was initiated by the addition of [γ⁻³²P]ATP (10 µM final concentration) and continued for 60 s at 37°C. Cyclic AMP (5 µM) was added 10 s prior to adding ATP. Theophylline (THEO), when present, was 4 mM. The incubation was terminated by the addition of 40 µl of a solution containing sodium dodecyl sulfate (6%), dithiothreitol (0.24 M), and pyronin-Y (60 µg/ml). Incubation at 37°C was continued for 35 min, and two 100-µl aliquots of each sample were subjected to polyacrylamide gel electrophoresis in 1% sodium dodecyl sulfate. Pictured is the reversed image of the radioautograph. TD, tracking dye.
Adipocytes were incubated at 37°C for 2 hours in the presence of NaH₂¹⁴PO₄. Aliquots of the entire suspension were then added to vessels containing insulin (final concentration 100 microunits/ml) or no addition for a further 5 min. The samples were subsequently processed and analyzed as described in Table I. The number of individual experiments yielding such paired comparisons is given in parentheses. The data are expressed as the per cent change in ¹⁴P content from control due to insulin ± S.E. of the difference.

### Table III

| Peptide molecular weight x 10⁻⁴ | Homogenate (n = 9) | Cytoplasm (n = 12) | Endoplasmic reticulum (n = 12) | Plasma membrane (n = 10) | Mitochondria (n = 5) |
|--------------------------------|-------------------|-------------------|-------------------------------|-------------------------|---------------------|
| 216                            | 9.6 ± 5.4         | 7.3 ± 2.7*        |                                |                         |                     |
| 123                            | 35.8 ± 5.4*       | 32.3 ± 10.2*      | 36.7 ± 10.2*                  |                         |                     |
| 94                             | 4.6 ± 3.0         | -7.8 ± 4.8        | 1.9 ± 3.6                     |                         |                     |
| 79                             | 4.0 ± 3.1         | -4.4 ± 3.3        | -8.4 ± 4.3                    |                         |                     |
| 69                             | 9.5 ± 6.3         | 3.9 ± 6.7         | 0.2 ± 4.3                     | 8.1 ± 4.4               |                     |
| 62                             | 7.3 ± 4.4         | -6.7 ± 4.8        | -3.1 ± 3.9                    | 4.2 ± 4.8               |                     |
| 50                             |                   |                   |                               |                         |                     |
| 46                             | 5.7 ± 4.4         |                   | 3.8 ± 5.0                     | 1.0 ± 7.5               |                     |
| 44                             | 5.4 ± 6.3         | -2.1 ± 5.8        | 1.8 ± 6.6                     | 1.4 ± 5.6               |                     |
| 41                             |                   |                   |                               |                         |                     |
| 34                             | 4.0 ± 10.9        |                   | -4.8 ± 6.3                    | 8.0 ± 6.6               |                     |
| 21                             |                   | 2.1 ± 6.4         |                               |                         |                     |
| 17                             |                   |                   | -1.3 ± 5.7                    |                         |                     |

* p < 0.05.  
* p < 0.001  
* p < 0.01.

The effect of insulin on the phosphorylation of the 123,000 peptide appeared to be dose-dependent and was detectable with 5 microunits/ml of insulin, the lowest concentration tested (data not shown). The insulin-induced increase in phosphorylation apparent after 5 min persisted unaltered for 15 min (data not shown).

A second effect of insulin on the phosphorylation of adipocyte peptides was observed in the presence of epinephrine. When ¹⁴P-labeled adipocytes were exposed to insulin (100 microunits/ml) and epinephrine (1 μM) simultaneously for 5 min, the epinephrine-stimulated phosphorylation of the 69,000-dalton peptide was partially inhibited by insulin, as was the epinephrine-stimulated phosphorylation of the plasma membrane phosphopeptide of molecular weight 26,000 (Table IV). In marked contrast, the phosphorylation of the 123,000-dalton peptide, which was augmented both by insulin and epinephrine individually, exhibited stimulation of ¹⁴P incorporation when both hormones were present simultaneously that significantly exceeded that induced by either hormone alone and was statistically indistinguishable from the sum of the increments induced by each agent alone (Table IV).

### DISCUSSION

The results reported clearly demonstrate that it is possible to detect acute hormonally induced changes in protein phosphorylation in intact cells. The rapidity and selectivity of these changes strongly support the concept that they reflect alterations in the activity of protein kinases and protein phosphatases, or both, rather than alternative mechanisms, such as changes in ¹⁴P incorporation into mononucleotides, intracellular ATP levels, or protein synthesis and degradation (5, 6).

Three types of evidence indicate that the enhanced phosphorylation of at least the peptides of molecular weight 123,000 and 69,000 caused by epinephrine was mediated by increased intracellular cyclic AMP and stimulation of the cytoplasmic cyclic AMP-dependent protein kinase (7). First, qualitatively similar effects are reproduced by a variety of agents known to increase intracellular cyclic AMP (8, 9); second, the stimulation of ¹⁴P incorporation obtained in the presence of submaximal concentrations of both epinephrine and theophylline is synergistic (10); and finally, the observation that endogenous peptides of identical molecular weight are substrates in vitro for the endogenous cyclic AMP-dependent protein kinase. These arguments cannot at present be extended rigorously to the remainder of peptides showing epinephrine-stimulated phosphorylation in intact adipocytes. Nevertheless, the observation that epinephrine enhances the phosphorylation of a large number of adipocyte peptides is not due to analytic bias, as indicated by the absolute selectivity of insulin-stimulated phosphorylation in parallel experiments and is compatible with current concepts of the mode of action of epinephrine. In fact, since our analysis is limited to the most prominent phosphopeptides, we may have overlooked entirely quantitatively minor phosphorylations of great functional significance. Furthermore, it is likely that our data underestimate the magnitude of the changes occurring in the intact cell. Soderling et al. (11) reported that the basal activity ratio of the cyclic AMP-dependent protein kinase in fat cells was 0.4, as opposed to 0.15 to 0.2 for fat pads. Thus, the preparation of isolated fat cells may itself engender a slight activation of this enzyme and diminish the apparent stimulation by hormone. In addition, the analytic techniques employed (i.e. polyacrylamide gel electrophoresis in sodium dodecyl sulfate) do not allow absolute resolution of epinephrine-responsive phosphopeptides from adjacent or superimposed unresponsive phosphopeptide moieties. Finally, and most important, the washing procedure employed in freeing cells from the medium after exposure to hormones requires 4 to 5 min, and this may be sufficient to allow the partial or complete decay of certain hormonally induced changes.

In summary, we have demonstrated that epinephrine stimulates the phosphorylation of a large number of peptides in...
Effects of epinephrine and insulin on adipocyte peptide phosphorylation

Adipocytes were incubated at 37°C for 2 hours in the presence of NaH\textsubscript{2}PO\textsubscript{4}. Aliquots of the entire suspension were then added to vials containing either insulin (100 microunits/ml, final concentration), epinephrine (1 µM, final concentration), insulin (100 microunits/ml) plus epinephrine (1 µM), or no addition (control). After further incubation for 5 min, the adipocytes were processed and analysed as described in Table I. The effects of insulin, epinephrine, and insulin plus epinephrine, respectively, were compared to the control, expressed as the per cent change from control. The number of experiments in which these paired observations were made is given in parentheses. Statistical analysis was carried out using Student's t test modified for paired data. The asterisk indicates that the change in \textsuperscript{32}P content in these peptides observed in the presence of epinephrine and insulin simultaneously is significantly different (p < 0.02) than the change in \textsuperscript{32}P content caused by epinephrine alone.

| Molecular weight (×10\textsuperscript{3}) | Insulin | Epinephrine | Both agents |
|------------------------------------------|---------|-------------|-------------|
| 100 microunits/ml                        | 1 µM    |             |             |
| 216                                      | 11.6 ± 7.1 | 27.0 ± 13.4 | 38.4 ± 11.8 |
| 123                                      | 35.1 ± 8.2 | 36.9 ± 6.4 | *74.9 ± 10.9* |
| 94                                       | 5.7 ± 4.6  | 12.9 ± 7.9  | 19.7 ± 5.3  |
| 79                                       | 8.3 ± 4.6  | 24.4 ± 6.7a | 31.1 ± 4.1  |
| 69                                       | 7.4 ± 3.4  | 91.3 ± 9.4  | *56.3 ± 8.8* |
| 62                                       | 10.4 ± 5.3 | 32.0 ± 6.8  | 28.1 ± 3.6a |
| 46                                       | 9.0 ± 5.2  | 22.4 ± 7.5a | 30.7 ± 6.1a |
| 41                                       | 8.6 ± 5.2  | 18.4 ± 4.3  | 18.8 ± 4.0a |
| 26                                       | 8.1 ± 14.4 | 34.0 ± 11.2 | 21.4 ± 4.0a |

| Plasma membrane peptide (n = 6) | Insulin |Epinephrine | Both agents |
|--------------------------------|---------|-------------|-------------|
| 79                             | 9.7 ± 11.4 | 0.2 ± 8.1  | 25.6 ± 21.6 |
| 62                             | 0.2 ± 8.0  | 8.5 ± 6.8  | 19.0 ± 9.7  |
| 26                             | 0.3 ± 10.4 | 19.0 ± 6.1  | *6.7 ± 9.3  |

\*p < 0.02.  
\*p < 0.01.  
\*p < 0.001.  
\*p < 0.05.

The intracellular localization of the 123,000-dalton peptide suggests by analogy that insulin may generate an as yet unidentified "second messenger" that modifies the activity of a protein kinase, protein phosphatase, or both. The list of potential candidates is of course quite large, and further speculation is not warranted. The existence of a "second messenger" unique to insulin was previously suggested from studies in liver (12) and muscle (13).

In support of the present observations, Benjamin and Singer (14, 15) recently reported that epinephrine stimulated the phosphorylation of an adipocyte peptide of molecular weight 60,000 to 65,000, an effect partly inhibited by insulin, whereas insulin alone stimulated the phosphorylation of a peptide of molecular weight 140,000.

Taken together, these findings clearly document an action of insulin that is mediated independently of cyclic AMP (and thus analogous to certain other insulin effects, e.g. on glucose transport, pyruvate dehydrogenase activity, etc.) and that appears to proceed concurrently with actions mediated by a lowering of intracellular cyclic AMP. Certain effects of both classes are expressed at the level of protein phosphorylation. It appears that a fuller understanding of the mechanisms by which insulin regulates protein phosphorylation may yield insights of general significance for the mechanism of this hormone's action.

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