Central and peripheral haemodynamic effects of hyperglycaemia, hyperinsulinaemia, hyperlipidaemia or a mixed meal

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ABSTRACT

The aim of the present study was to evaluate the haemodynamic changes during hyperinsulinaemia, hyperglycaemia or hypertriglyceridaemia in relation to those following a mixed meal. Ten subjects were subjected to hypertriglyceridaemia (3.9 mmol/l) for 2 h by an infusion of Intralipid® and heparin. Nine subjects received a hyperglycaemic clamp (12.5 mmol/l) with octreotide and low-dose insulin infusion to maintain normoinsulinaemia (10 m-units/l). Ten subjects received saline for 2 h as a control and, thereafter, 2 h of normoglycaemic hyperinsulinaemic clamp (80 m-units/l). Finally, ten subjects were evaluated for 2 h following an ordinary mixed meal. Calf blood flow was measured by venous occlusion plethysmography and cardiac index by thoracic bioimpedance. Both the mixed meal and normoglycaemic hyperinsulinaemia lowered total peripheral resistance, and increased calf blood flow and cardiac index, whereas blood pressure decreased (P < 0.05–0.001). Both hyperglycaemia and hypertriglyceridaemia increased calf blood flow, but blood pressure was unchanged. Total peripheral resistance was unchanged in hypertriglyceridaemia, whereas hyperglycaemia induced a significant increase. Normoglycaemic hyperinsulinaemia induced a haemodynamic pattern similar, but to a lesser extent, to the pattern seen following a mixed meal. Hyperinsulinaemia seems to be a major mediator of the haemodynamic response, but other factors are obviously also of great importance. Hypertriglyceridaemia and hyperglycaemia induced haemodynamic responses that are not similar to those seen following a mixed meal.

INTRODUCTION

A mixed meal induces vasodilation in several vascular beds, for example skeletal muscle, the splanchnic area and adipose tissue [1–5]. Furthermore, a mixed meal is associated with an elevated cardiac output, which contributes to a maintained blood pressure and facilitates delivery of substrates and hormones to the liver and peripheral tissues. This is followed by a multihormonal response, which is paralleled by alterations in the circulating concentrations of nutrients. The major alterations following a mixed meal are an elevation in circulating insulin levels together with raised concentrations of blood glucose and serum triacylglycerols (triglycerides).

Although the peripheral haemodynamic effects of hyperglycaemia, hyperinsulinaemia and hypertriglyceridaemia have been reported previously [6–11], data on both central and peripheral haemodynamics during these three different metabolic conditions are limited. Therefore, in the present study, central and peripheral haemodynamics were studied during 2 h of normoinsulinaemic hyperglycaemia, normoglycaemic hyperinsulinaemia or

Key words: blood flow, glucose, haemodynamics, insulin, lipids.
Abbreviations: CBF, calf blood flow; CI, cardiac index; HR, heart rate; LVR, leg vascular resistance; MAP, mean arterial pressure; NEFA, non-esterified fatty acid; TPR, total peripheral resistance; TPRi, TPR index.
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hypertriglyceridaemia induced in young healthy volunteers and compared with the haemodynamic response seen during 2 h following a mixed meal.

MATERIAL AND METHODS

Subjects
All subjects were young, apparently healthy and normotensive students without a history of diabetes or other metabolic disorders and were without regular medication. All showed fasting normoglycaemia. Basal characteristics of the groups engaged in the different metabolic studies are shown in Table 1. The subjects in the saline-control protocol were the same as in the normoglycaemic hyperinsulinaemic protocol. The study protocol was approved by the Human Ethics Committee of the Medical Faculty in Uppsala, and informed consent was obtained from all participants.

Experimental protocols and measurements
The studies began between 08.00 and 08.30 hours after an overnight fast. The subjects rested supine in a room at constant temperature (20-22 °C). The subjects received a catheter into an antecubital vein for infusions of glucose, octreotide, insulin and Intralipid (Pharmacia & Upjohn, Uppsala, Sweden). Another catheter was inserted into an antecubital vein of the opposite arm for blood sampling. In the mixed meal protocol, only the latter catheter was used. Calf blood flow (CBF), blood pressure, heart rate (HR) and cardiac index (CI) measurements and blood sampling, for baseline data, were performed after at least a 30 min rest following insertion of the catheters. Measurements of the haemodynamic parameters were then repeated at 10 min intervals during the first hour of all the experimental protocols. During the second hour, the measurements were performed at 30 min intervals. Samples for plasma insulin and serum triacylglycerols were collected at baseline and after 2 h.

CBF was measured by venous occlusion plethysmography. A mercury in-silastic strain gauge was placed at the upper third of the calf. The calf rested comfortably slightly above the level of the heart. A strain gauge was connected to a calibrated plethysmograph. Venous occlusion was achieved by a blood pressure cuff applied proximal to the knee and inflated to 40 mmHg by a rapid cuff inflator. CBF was determined from the mean of at least five consecutive recordings. The reproducibility of this measurement has been evaluated previously [12]. In that study [12], after 2 h of slow saline infusion or when repeated after 3 weeks during baseline conditions, CBF showed a variation of less than 10 %.

Blood pressure was monitored by an automatic device (OMRON® HEM 705C; Omron, Tokyo, Japan). Mean arterial pressure (MAP) was calculated as pulse pressure divided by three and added to the diastolic blood pressure. Leg vascular resistance (LVR) was calculated as the MAP divided by CBF. Total peripheral resistance (TPR) index (TPRI) was calculated as $80 \times (\text{MAP} - \text{3})/\text{CI}$. HR and cardiac output were measured by a thoracic bio-impedance cardiograph (BoMed® NCCOM® cardiodynamic monitor; BoMed Biomedical, Irvine, CA, U.S.A.) [13]. CI and TPRI were obtained by indexing for body surface area.

Based on previous experience, although the different haemodynamic changes may appear more rapidly, these changes usually last for 2 h and, for some of the variables, increase up to 2 h. Therefore the change from baseline to

<table>
<thead>
<tr>
<th>Study group</th>
<th>Normoinsulinaemic hyperglycaemia</th>
<th>Hyperinsulinaemic normoglycaemia</th>
<th>Hypertriglyceridaemia</th>
<th>Mixed meal</th>
</tr>
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<tbody>
<tr>
<td>Parameters</td>
<td></td>
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<td>$n$</td>
<td>9</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Males/females</td>
<td>3/6</td>
<td>7/3</td>
<td>6/4</td>
<td>5/5</td>
</tr>
<tr>
<td>Age (years)</td>
<td>23.4 ± 2.5</td>
<td>24.4 ± 3.1</td>
<td>24.2 ± 2.3</td>
<td>24.1 ± 1.8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 ± 7</td>
<td>179 ± 10</td>
<td>177 ± 11</td>
<td>174 ± 9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.8 ± 11.9</td>
<td>72.3 ± 6.2</td>
<td>71.2 ± 8.4</td>
<td>68.7 ± 9</td>
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<tr>
<td>BMI (kg/m$^2$)</td>
<td>23.7 ± 2.8</td>
<td>22.7 ± 2.4</td>
<td>22.7 ± 2.3</td>
<td>22.7 ± 2.8</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>79.7 ± 4.2</td>
<td>83.8 ± 8.5</td>
<td>81.5 ± 6.4</td>
<td>83.5 ± 7</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>57.9 ± 8.8</td>
<td>60.2 ± 13.8</td>
<td>57.7 ± 13.9</td>
<td>64.5 ± 11.2</td>
</tr>
<tr>
<td>TPRI (dynes s$^{-1}$ m$^{-2}$ cm$^{-1}$)</td>
<td>1727 ± 390</td>
<td>1910 ± 281</td>
<td>1754 ± 452</td>
<td>2053 ± 483</td>
</tr>
<tr>
<td>LVR (ml s$^{-1}$ m$^{-1}$, 100 ml$^{-1}$ mmHg$^{-1}$)</td>
<td>41.2 ± 9.2</td>
<td>43.1 ± 11.8</td>
<td>41.9 ± 8.7</td>
<td>42.0 ± 8.9</td>
</tr>
<tr>
<td>CI (l s$^{-1}$ m$^{-1}$)</td>
<td>3.7 ± 0.5</td>
<td>3.4 ± 0.5</td>
<td>3.8 ± 1.1</td>
<td>3.3 ± 0.8</td>
</tr>
<tr>
<td>CBF (ml s$^{-1}$ m$^{-1}$, 100 ml$^{-1}$)</td>
<td>2.0 ± 0.5</td>
<td>2.3 ± 1.4</td>
<td>2.0 ± 0.5</td>
<td>2.1 ± 0.5</td>
</tr>
</tbody>
</table>
2 h was chosen as the primary outcome measure for the different haemodynamic variables.

Plasma glucose was measured in duplicate in a Glucose Analyser 2 (Beckman, Fullerton, CA, U.S.A.). Insulin was assayed in EDTA plasma samples in duplicate using an enzymic immunological assay (Enzymun®; Boehringer Mannheim, Germany) performed in an ES300 automatic analyser (Boehringer Mannheim). Triacylglycerol concentrations in serum were assayed by enzymic techniques in a Monarch 2000 centrifugal analyser (Instrumentation Laboratories, Lexington, MA, U.S.A.).

Normoinsulinaemic hyperglycaemic protocol

After basal measurements, the somatostatin analogue octreotide (Sandostatin®; Sandoz, Switzerland) was infused for 2 h at 500 µg/h in order to suppress endogenous insulin release, followed by 2 h of normoinsulinaemic hyperglycaemia. During the latter period, the octreotide infusion (250 µg/h) was continued together with a constant low-dose insulin infusion (0.1 m-units·kg⁻¹·min⁻¹; Actrapid Human®; Novo Nordisk, Bagsvaerd, Denmark) calculated to restore the plasma insulin level to the basal fasting level. The glucose infusion started with a priming dose for 10 min and the rate was adjusted every fifth minute, according to measurements of plasma glucose, with a target plasma glucose concentration of 12–13 mmol/l.

Saline control protocol and normoglycaemic hyperinsulinaemia

This protocol started with 2 h of intravenous saline (0.9 % NaCl) infusion, followed by a 2 h normoglycaemic hyperinsulinaemic clamp [14]. A priming dose of insulin was given over 10 min and, thereafter, insulin was infused at a constant rate of 56 m-units·min⁻¹·m⁻² of body surface area. The plasma glucose concentration was determined at 5 min intervals. The rate of the glucose infusion (20 %, w/v) was adjusted in order to achieve a target plasma glucose concentration of 5.1 mmol/l. The coefficient of variation for plasma glucose was < 5 %.

Hypertriglyceridaemia protocol

During a 2 h intravenous infusion, Intralipid® (200 mg/ml) was given together with intermittent injections of heparin (Pharmacia & Upjohn). Intralipid® was given as a bolus dose of 0.5 ml/kg of body weight over 10 min and, thereafter, as a continuous infusion at a rate of 90 ml/h. Heparin was given every fifth minute at a dose corresponding to 150 units/h.

Mixed meal protocol

After baseline measurements, the subjects received a meal consisting of rice, minced meat sauce and vegetables. Males received 900 kcal and females 700 kcal (1 kcal = 4.184 kJ). The meal was followed by 250 ml of water. The meal contained 34 % energy as fat, 51 % energy as carbohydrate and 15 % energy as protein. Of the fat, 26 % was saturated, 38 % was mono-unsaturated and 36 % was polyunsaturated. The meal was ingested during 15 min and the first measurements were started 20 min after start of ingestion.

Statistics

Differences in the haemodynamic variables were evaluated by ANOVA for repeated measurements. A paired Student’s t test was used for post-hoc analysis. P < 0.05 was regarded as significant.

RESULTS

Values for plasma glucose, plasma insulin, serum triacylglycerols and serum non-esterified fatty acids (NEFAs) during the different metabolic conditions and the saline control are shown in Table 2.

Normoglycaemic hyperinsulinaemia

Normoglycaemic hyperinsulinaemia induced a significant decline in both calf vascular resistance as well as in TPR, which was significant after 10 min (Figure 1). The decline in LVR and TPR was accompanied by a significant increase in CI and CBF (Figure 2). MAP and HR at the end of the 2 h study period were unchanged compared with baseline, although a transient reduction in MAP was seen at 30 min (Figure 3). Glucose infusion rate during the last hour of normoglycaemic hyperinsulinaemia was 8.0 ± 0.5 mg·kg⁻¹·min⁻¹.

Normoinsulinaemic hyperglycaemia

Hyperglycaemia at basal insulin concentrations induced a significant increase in TPRI established after 40 min (Figure 1). LVR did not, however, change significantly. There was a tendency towards an increase in MAP at the end of the 2 h period (P = 0.056; Figure 3). On the other hand, CI declined as did HR (Figures 2 and 3). Glucose infusion rate during the last hour of normoinsulinaemic hyperglycaemia was 2.2 ± 0.4 mg·kg⁻¹·min⁻¹.

Hypertriglyceridaemia

Hypertriglyceridaemia tended to increase MAP (P = 0.08; Figure 3). This tendency towards an increased MAP was mainly due to a significant increase in CI (Figure 2), as well as a tendency towards an increase in TPRI (Figure 1). A significant increase in CBF was observed (Figure 2), whereas LVR decreased (Figure 1). HR did not change significantly.

Mixed meal

The mixed meal induced a significant decline in both TPRI and LVR, which was evident by 20 min (Figure 1). The vasodilation was paralleled by increments in both

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### Table 2 Plasma glucose, plasma insulin, serum triacylglycerols and serum NEFAs at baseline and after 2 h in the different study Protocols

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Study group</th>
<th>Baseline</th>
<th>2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>Saline</td>
<td>5.1 ± 0.2</td>
<td>4.9 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Normoglycaemic hyperinsulinaemia</td>
<td>0.06 ± 0.8</td>
<td>0.0 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Hypertriglyceridaemia</td>
<td>8.6 ± 4.2</td>
<td>8.0 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>Mixed meal</td>
<td>1.0 ± 0.3</td>
<td>0.88 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>Normoinsulinaemic hyperglycaemia</td>
<td>24 ± 11</td>
<td>24 ± 10</td>
</tr>
<tr>
<td>Serum insulin (m-units/l)</td>
<td></td>
<td>0.09 ± 0.2</td>
<td>0.09 ± 0.3</td>
</tr>
<tr>
<td>Serum triacylglycerols (mmol/l)</td>
<td></td>
<td>0.90 ± 0.21</td>
<td>0.92 ± 0.39</td>
</tr>
<tr>
<td>Serum NEFAs (mmol/l)</td>
<td></td>
<td>0.43 ± 0.35</td>
<td>0.43 ± 0.35</td>
</tr>
</tbody>
</table>

Values are means ± S.D. Hypertriglyceridaemia is Intralipid® + heparin. ∗P < 0.05, ∗∗P < 0.01 and ∗∗∗P < 0.001 compared with baseline.

### Figure 1 Changes in TPRI (upper panel) and LVR (lower panel) at various time points during the different metabolic conditions in the study

Baseline absolute levels are given in Table 1. Data are means ± S.E.M. ∗P < 0.05 and ∗∗∗P < 0.001 compared with baseline, as determined by ANOVA for repeated measurements.

The increase in CI induced by the mixed meal was mainly due to a significant increase in HR (Figure 3). Despite the increase in CI, there was a small, but significant, reduction in MAP during the latter part of the 2 h period (Figure 3).

### Saline control protocol

No significant changes in any of the studied variables were seen during the 2 h of saline infusion. (Figures 1–3).

### DISCUSSION

The present study shows that hyperinsulinaemia, hypertriglyceridaemia and hyperglycaemia induced three different types of haemodynamic patterns in healthy volunteers.

Of the three different metabolic conditions used in the present study, the haemodynamic pattern induced by normoglycaemic hyperinsulinaemia was most closely
related to that seen following a mixed meal. The vaso-
dilation induced by the mixed meal was more marked
than during hyperinsulinaemia, despite a more than a
2-fold elevation of plasma insulin during the normo-
glycaemic hyperinsulinaemic clamp compared with the
mixed meal. Thus, although hyperinsulinaemia seems
to be a major factor inducing postprandial haemo-
dynamic changes, other factors must also be of
importance. This is in line with the finding [15,16] that
oral intake of glucose leads to a more marked increase
in muscle nerve sympathetic activity than after elevation
of plasma insulin during a normoinsulinaemic clamp.
This indicates that muscle nerve sympathetic activity as
well as the haemodynamic changes are stimulated not
only by insulin, but also by mechanisms originating from
exposure of the gastrointestinal tract to food or nutrients.

Our present results suggest that neither hyper-
glycaemia nor hypertriglyceridaemia contribute to the
general vasodilation seen following a mixed meal. The
level of hyperglycaemia and hypertriglyceridaemia
induced in the present study, however, by far exceeds
that seen following a mixed meal. Therefore it cannot be
excluded that other haemodynamic patterns would be
found during more modest elevations of these two
nutrients. However, a low-dose infusion of Intralipid®
also raised systolic blood pressure in a recent study
[10]. The design of the present study, with intravenous
administration of the different protocols dealing with
the effects of hyperinsulinaemia, hyperglycaemia and
hyperlipidaemia, was considered appropriate when
trying to separate the haemodynamic actions of these
two metabolic conditions. If, for example, glucose was
given orally, it would have been very hard to separate
the haemodynamic actions of glucose and insulin.

A general vasodilation, also including limb blood
flow, has been described by several investigators
during normoglycaemic hyperinsulinaemia [8,9]. The
vasodilation is accompanied by a rise in CI in order to
maintain a constant blood pressure to increase hormone
and substrate availability in peripheral insulin-sensitive
tissues. When administered intravenously, insulin ac-
tivates the sympathetic nervous system, as evaluated
by both raised levels of circulating noradrenaline and
recordings of peripheral nerve activity [15], which occur
in parallel with these haemodynamic changes. The exact
physiological importance of this increase in sympathetic
nervous system activity is, however, not fully understood,
but its purpose may be to counteract the effects of the pronounced vasodilation.

In the present study, we found that hyperglycaemia increased peripheral vascular resistance but, due to a reduced CI, only a tendency to increased MAP was seen. Thus, apart from the increase in CBF facilitating the availability of glucose in the skeletal muscle of the leg, the other components of the haemodynamic pattern induced by hyperglycaemia were different from those seen following a mixed meal. Other investigators [17] have, in contrast with the present study, observed a more marked increase in MAP as well as in HR under similar hyperglycaemic normoinsulinaemic conditions. The reasons for this discrepancy are not clear, but may be due to an overshoot in the compensation to skeletal muscle vasodilation.

Octreotide, which has known vasoactive properties, could be interfering with the haemodynamic pattern during hyperglycaemia; however, other investigators [6,18] have found no interference by octreotide on the HR and MAP under similar experimental settings.

As with the other metabolic conditions in the present study, hypertriglyceridaemia increased CBF, in accordance with previous observations [10,19]. As with hyperglycaemia, hypertriglyceridaemia did not change MAP significantly, although a tendency towards increased MAP was seen. The mechanism behind the trend to increased blood pressure induced by hypertriglyceridaemia is not known. It cannot be excluded that the elevated levels of NEFAs may underlie the haemodynamic actions, rather than the elevated levels of serum triacylglycerols. Infusion of NEFAs has been shown to activate the sympathetic nervous system [20] and to increase the sensitivity to vasopressor agents such as noradrenaline [21]. NEFA levels have also been found to be related both to endothelial vasodilatory function [10,22] and to the ability of insulin to promote vasodilation [23].

Preliminary data from our own studies using different proportions of fat, carbohydrate and proteins in mixed meals with the same amount of energy suggest that the proportion of different nutrients are of modest importance, as the haemodynamic response tends to be very similar for all meals (A. Fugmann, J. Millgård, M. Sarabi, C. Berne and L. Lind, unpublished work). Thus the content of naturally occurring vasodilators in food, such as l-arginine, does not seem to play a critical role for the postprandial haemodynamic action of the meal.

Other investigators [24,25] have also found that the ingestion of a meal results in an increased forearm blood flow or leg blood flow. Muller et al. [24] observed an increased CBF after a 800 kcal meal in healthy young subjects. Hoost et al. [25] observed an increased forearm blood flow after meals consisting predominantly of carbohydrate or protein, but not after a meal consisting predominantly of fat.

In contrast, Hernandez Mijares and Jensen [26] found no significant increase in limb blood flow after a mixed meal. The plasma insulin response in the study by Hernandez Mijares and Jensen [26] also showed a 12-fold increase when the peak level was compared with the fasting level. In our present study, this increase was only approx. 4-fold. It is not likely that the composition of the meal consumed in that study [26] can be the cause of this discrepancy, as the meal in our present study had an almost identical fat, protein and carbohydrate content. A major difference was, however, that the meal in our present study was not fluid as in the study by Hernandez Mijares and Jensen [26]. Since a liquid meal ought to lead to a more rapid increase in blood glucose and, therefore, also in plasma insulin levels, it is interesting that no increase in leg blood flow was observed.

One limitation of the present study is that a parallel-group design was used and not a cross-over design in which the same subjects would receive all four interventions. This was, however, not possible due to practical reasons. Therefore the gender distribution was slightly different in the different groups. This might have influenced the results to some degree, as it has been shown that young females have a more pronounced response to insulin compared with males [27,28]. Another limitation is that the three metabolic interventions induced more pronounced metabolic changes than usually seen following a mixed meal. It was, however, our aim to create clear-cut haemodynamic changes during the three metabolic interventions in order to separate these effects, so therefore pronounced metabolic effects were induced.

In conclusion, normoglycaemic hyperinsulinaemia induced a reduction in TPR as well as an increase in CBF, together with an increase in cardiac output in order to maintain a constant blood pressure. This haemodynamic pattern was similar, but less pronounced, when compared with that seen following a mixed meal. Normoinsulinaemic hyperglycaemia and hypertriglyceridaemia both increased CBF, but did not induce vasodilation, because of a tendency to also increase blood pressure. Thus it seems likely that an increase in insulin is a major mediator of the haemodynamic changes seen following a mixed meal.

REFERENCES


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