Role of lipids in the early developmental stages of experimental immune diabetes induced by multiple low-dose streptozotocin

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Pighin, Dario, Liliana Karabatas, Claudia Pastorale, Eduardo Dascal, Cecilia Carbone, Adriana Chicco, Yolanda B. Lombardo, and Juan Carlos Basabe. Role of lipids in the early developmental stages of experimental immune diabetes induced by multiple low-dose streptozotocin. J Appl Physiol 98: 1064–1069, 2005; doi:10.1152/japplphysiol.00559.2004.—The present work examines the role of lipids in the development of Type 1 diabetes induced by the administration of multiple low doses of streptozotocin (STZ) in C57BL/6J mice. The study was performed before and after the onset of clear hyperglycemia, and the results were as follows. First, 6 days after the first dose of STZ, while plasma glucose and insulin levels remained similar to those observed in the control mice, plasma free fatty acid (FFA) levels were significantly increased (P < 0.05). At that time, a marked increase of triglyceride content in gastrocnemius muscle was accompanied by a diminished activity of pyruvate dehydrogenase complex, suggesting an impaired glucose oxidation. Furthermore, a decrease of both triglyceride content and lipoprotein lipase activity was observed in the epididymal fat tissue. Second, 12 days after the first injection of STZ, hyperglycemia was accompanied by hypertriglyceridemia, a more pronounced increase of plasma FFA, and a significant (P < 0.05) reduction of insulinemia. At this time, both the adipose tissue and the gastrocnemius muscle showed a further deterioration of all parameters mentioned after 6 days. Moreover, in the gastrocnemius muscle, an impaired nonoxidative pathway of glucose metabolism was observed [significant reduction (P < 0.05) of glycogen mass, glucose-6-phosphate content, and glycogen synthase activities] at this time point. Finally, the data suggest for the first time that, in mice, Type 1 diabetes induced by multiple low doses of STZ and enhanced lipolysis of fat pads leads to an increase in the availability of plasma FFA, which seems to play a role in the early steps of diabetes evolution.

experimental diabetes; lipids; free fatty acids; triglycerides; insulin secretion

INSULIN-DEPENDENT DIABETES MELLITUS (IDDM), or Type 1 diabetes, is a chronic disorder that results from the autoimmune destruction of the insulin-producing pancreatic β-cells. Several animal models have been developed that allow the investigation of islet pathology, leading to autoimmune diabetes mellitus in vivo. Among them, the BB rats and NOD mice are genetic spontaneous models of the disease (14, 19). Moreover, the repeated administration of multiple low doses of streptozotocin (mld-STZ) to susceptible strains of mice produces insulinis-related diabetes (24). The diabetic syndrome induced in C57BL/6J mice by mld-STZ mimics in some basic aspects of recent-onset Type 1 diabetes in human patients. Earlier events have been described in this experimental model since Wang and Gleichman (40) found a progressive decrease of GLUT2 protein and mRNA expression in pancreatic islets from C57BL/6J male mice with mld-STZ on day 4 after the first streptozotocin injection, which clearly preceded the onset of hyperglycemia. Our laboratory has recently demonstrated (18) that islets from mld-STZ of C57BL/6J mice show increases in apoptotic cells already at day 4 after the first injection of the diabetogenic drug. Moreover, isolated or microfocal cell death and insulitis are present from day 6, whereas moderate hyperglycemia and diminished insulin secretion from in vitro perfused pancreatic islets appear at day 9 after mld-STZ.

It is well known that IDDM is a disease that reflects a variety of genetic, environmental (e.g., dietary constituents), and immunological factors (5). Both β-cell dysfunction and insulin resistance are also present in IDDM, although differences with non-IDDM can be observed in the kinetics of their appearance (17). Recently, Ebeling et al. (11) showed that IDDM is associated with increased intramuscular triglyceride content. Patients with IDDM have elevated basal lipid oxidation rates, which is in agreement with their insulin resistance. Also, an increase of both adipose tissue lipolysis and free fatty acid (FFA) mobilization was observed in the early stages of insulin deficiency (35). On the other hand, Linn et al. (25), working with NOD mice fed a fat-rich diet, demonstrated that progression to diabetes was associated with impairment of insulin-stimulated whole body glucose disposal, thus suggesting that insulin action may also be relevant to diabetes progression even in the presence of normoglycemia. At present, the role of lipids in the development of Type 1 diabetes has not been extensively studied. However, although plasma lipid levels could be normal before the onset of hyperglycemia, once insulin deficiency develops, plasma fatty acid levels in addition to glucose go up and consequently may cause β-cell glucotoxicity. This process could impair the function of residual β-cells, and this could be particularly important at the onset of the disease (31).

The aim of the present work was to analyze the role of lipids in the development of Type 1 diabetes induced by mld-STZ administration in C57BL/6J mice. To achieve this goal, the following items were evaluated before and after the onset of hyperglycemia: 1) the temporal evolution of plasma triglyceride and FFA levels, 2) the possible changes in the oxidative and nonoxidative pathways of glucose metabolism in the gastrocnemius muscle (a target tissue of insulin action), and

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the contribution of adipose tissue to these changes. Plasma insulin levels and glucose stimulated insulin secretion in perfused islets were also evaluated at the same time periods.

**MATERIALS AND METHODS**

**Animals.** Aging (2.5–3.0 mo old) male C57BL/6J inbred mice weighing 23–26 g were obtained from the Department of Radiology, National Atomic Energy Commission (Buenos Aires, Argentina). Animals were maintained in a room under controlled temperature (23°C), humidity, and air-flow conditions, with a fixed 12-h light-dark cycle. Mice had free access to water and a standard laboratory chow (Carhill, Buenos Aires, Argentina). The protocols of animal use were approved by the Human and Animal Research Committee of the School of Biochemistry, University of Litoral (Santa Fe, Argentina).

**Experimental design.** After a 1-wk period of acclimatization, non-fasted C57BL/6J mice were injected with 0.1 ml citrate buffer ip (0.1 M trisodium citrate, 0.1 M citric acid, pH = 4.5) or 40 mg/kg body wt of streptozotocin (Sigma, St. Louis, MO) dissolved in 0.1 ml of citrate buffer for 5 consecutive days (mld-STZ). Animals were killed by cervical dislocation at days 4 (before the 4th injection), 6, and 12 after the first injection of streptozotocin or buffer alone. The weight and energy intake of each mouse were recorded every day during the experimental period.

**Analytical methods.** Blood samples were obtained from cardiac puncture and immediately centrifuged at 4°C. The plasma samples obtained were immediately assayed or stored at −20°C and examined within the following 3 days. Plasma glucose (2), triglycerides (23), and FFA (39) were determined by spectrophotometric methods. Immunoreactive insulin was measured by Herbert et al.’s methods (16).

**Pork monoiodine**

125I-insulin was obtained from CENEXA, School of Medicine, University of La Plata, Argentina. The rat insulin standard was obtained from Novo Nordisk (Copenhagen, Denmark). Guinea pig anti-porcine insulin antiserum (Sigma) was sufficiently nonspecific to allow pork-labeled insulin to be displaced by mouse and rat insulin.

**Medicine, University of La Plata, Argentina.** The rat insulin standard was measured by the method of Folch et al. (12). The gastrocnemius muscle was rapidly removed from all the animals and frozen. The extraction of PDHc from the gastrocnemius muscles has been previously described in detail (9).

**Glycogen synthase activity.** In vitro glycogen synthase activity (GSA) was determined by the method of Golden et al. (13). The glycogen synthase independent activity was the activity measured at low G-6-P concentration, and the total GSA was the activity measured at high G-6-P concentration. The fractional velocity of glycogen synthase was calculated as the rate of incorporation of labeled [U-14C]uridine-diphosphoglucose into glycogen at 0.1 mM G-6-P divided by the rate at 10 mM and expressed as a percentage (15).

**Statistical analysis.** Results are expressed as means ± SE. The statistical significance between groups was determined by analysis of variance, followed by inspection of all differences between pairs of

**Table 1. Plasma metabolites and insulin concentration in control or mld-STZ-injected mice**

<table>
<thead>
<tr>
<th>Days After First Injection</th>
<th>Free Fatty Acids, mM</th>
<th>Triglyceride, mM</th>
<th>Glucose, mM</th>
<th>Insulin, µU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control mice</td>
<td>6</td>
<td>362.8±27.0 ²</td>
<td>1.06±0.07 ³</td>
<td>9.24±0.29 ³</td>
</tr>
<tr>
<td>mld-STZ mice</td>
<td>6</td>
<td>689.0±59.7 ²</td>
<td>1.03±0.04 ³</td>
<td>10.00±0.31 ³</td>
</tr>
<tr>
<td>Control mice</td>
<td>12</td>
<td>399.0±25.2 ²</td>
<td>1.03±0.06 ³</td>
<td>9.88±0.36 ³</td>
</tr>
<tr>
<td>mld-STZ mice</td>
<td>12</td>
<td>1,119.5±55.2 ²</td>
<td>1.68±0.03 ³</td>
<td>23.66±0.70 ³</td>
</tr>
</tbody>
</table>

²×²ANOVA

Values are means ± SE; n = 8 animals per experimental group. mld-STZ, multiple low-dose streptozotocin. S, effect significant (P < 0.05). Values in each column that do not share a superscript letter differ (P < 0.05) when one variable at a time was compared by Newman-Keuls test.
means by the Newman-Keuls’ test (34). Differences with P values of <0.05 were considered statistically significant.

Reagents. Enzyme for the assays, substrate, and coenzymes were purchased from Sigma or Boehringer Mannheim Biochemical (Indianapolis, IN). Uridin-5’-diphospho [U-14C]glucose was purchased from New England Nuclear (Boston, MA). All other chemicals were reagent grade.

RESULTS

Plasma metabolites and insulin levels. Only a significant increase of plasma FFA levels was recorded in mice injected with mld-STZ 6 days after the first injection compared with age-matched controls, which received citrate buffer. A different picture emerged after 12 days, in which plasma triglyceride, FFA, and glucose levels were significantly higher in mld-STZ mice compared with control mice (Table 1). This was accompanied by a significant reduction of plasma insulin levels.

It is worth noticing that, in mld-STZ mice at day 4 postinjection, all the above parameters were similar to those recorded in the control mice (data not shown).

Muscle metabolites and glycogen synthase, PDHc, and PDH-kinase activities. The gastrocnemius muscle of mld-STZ mice at 12 days after the first injection shows a significant decrease (P < 0.05) of glycogen and G-6-P contents compared with control mice injected with citrate buffer. Furthermore, the glycogen synthase activity, expressed as percent of fractional activity, was significantly lower (P < 0.05) in this group of mice. The above changes were not observed at day 6 after the first injection (Table 2). No changes in total GSA were recorded either in the control mice or in mld-STZ mice either at day 6 or day 12 postinjection (data not shown).

The muscle triglyceride content significantly increased (P < 0.01) at day 6 after the first mld-STZ injection. This was accompanied by both a reduced active form of the PDHc and an increase of PDH-kinase activities, suggesting an impaired glucose oxidation. A further increase in muscle triglyceride content and a decrease of the active form of the PDHc activity was recorded in mld-STZ mice 12 days after the first injection (Table 3). Moreover, the total PDHc activity expressed per gram of wet tissue did not differ among the groups. Values were as follows (in U/g wet tissue; means ± SE; n = 6): control mice 0.83 ± 0.057; mld-STZ mice 0.79 ± 0.06 and 0.86 ± 0.08 at 6 and 12 days after the first injection, respectively. Similar results were obtained when the values were expressed per milligram of protein or per unit of citrate synthase.

Fat pad weight, triglyceride content, and LPL and G-6-P dehydrogenase activities. The epididymal tissue weight significantly decreased (P < 0.05) in mice treated with mld-STZ after either 6 or 12 days of the first injection compared with control mice. Fat pad triglyceride content was also significantly reduced (P < 0.05) at the same time period (Table 4).

Compared with control mice, a significant reduction of fat pad LPL activity (mU/total weight) was observed both 6 and 12 days after mld-STZ injection, whereas the G-6-P dehydrogenase activity (U/total weight) was significantly decreased (P < 0.05) only after 12 days (Table 4). Furthermore, at days 6 and 12 after the first mld-STZ injection, the reduction of epididymal fat weight is accompanied by a decrease of body weight. Values were as follows (in g; means ± SE; n = 8): initial body weight: 25.8 ± 0.4; 6 days after the first injection: control mice: 26.7 ± 0.20, mld-STZ mice: 24.7 ± 0.45 (P < 0.05); 12 days after the first injection: control mice: 27.8 ± 0.38, mld-STZ mice: 23.5 ± 0.52 (P < 0.05). No significant changes in body weight were observed between 6 and 12 days after mld-STZ injection, and the energy intake of both mld-STZ and control groups of mice was similar between days 1 and 6 after the first injection. However, from days 6 to 12, the energy intake was increased almost twofold in mld-STZ mice compared with the control group. Values were as follows (in kJ/day; mean ± SE; n = 8): control: 74.5 ± 4.3; 6 days after mld-STZ: 84.1 ± 5.2; and 12 days after mld-STZ: 116.2 ± 6.6 (P < 0.05, day 12 vs. day 6 and control).

<table>
<thead>
<tr>
<th>Glycogen Synthase Activity, µmol/g wet wt</th>
<th>Glycogen Synthase Activity, % of Total Activity</th>
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<tbody>
<tr>
<td>Control mice 12 days after citrate buffer injection</td>
<td>16.03 ± 1.09a</td>
</tr>
<tr>
<td>6 days after 1st injection mld-STZ mice</td>
<td>15.10 ± 0.58a</td>
</tr>
<tr>
<td>12 days after 1st injection mld-STZ mice</td>
<td>10.00 ± 1.30b</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6 animals per experimental group. Values in each column that do not share a superscript letter differ (P < 0.05) when one variable at a time was compared by Newman-Keuls test. PDH, pyruvate dehydrogenase; PDHc, PDH complex; PDHa, active form of PDH complex, expressed as the percentage of total PDHc activity (basal activity × 100/total activity). PDH-kinase activity was assayed as determining the ATP-dependent inactivation of PDHc activity as function of time (K, min⁻¹) and was calculated from the first-order kinetic constant.

Table 3. Triglyceride concentration, PDHc, and PDH-kinase activities in gastrocnemius muscle of control or mld-STZ-injected mice

<table>
<thead>
<tr>
<th>Triglyceride, µmol/g wet wt</th>
<th>PDHα, % of total PDH</th>
<th>PDH Kinase, K, min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control mice 12 days after citrate buffer injection</td>
<td>4.30 ± 0.61a</td>
<td>34.70 ± 2.90a</td>
</tr>
<tr>
<td>6 days after 1st injection mld-STZ mice</td>
<td>6.80 ± 0.44b</td>
<td>21.20 ± 3.12b</td>
</tr>
<tr>
<td>12 days after 1st injection mld-STZ mice</td>
<td>11.40 ± 0.9b</td>
<td>12.90 ± 1.6b</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 6 animals per experimental group. Values in each column that do not share a superscript letter differ (P < 0.05) when one variable at a time was compared by Newman-Keuls test. PDH, pyruvate dehydrogenase; PDHc, PDH complex; PDHa, active form of PDH complex, expressed as the percentage of total PDHc activity (basal activity × 100/total activity). PDH-kinase activity was assayed as determining the ATP-dependent inactivation of PDHc activity as function of time (K, min⁻¹) and was calculated from the first-order kinetic constant.
Insulin secretion from perfused islets. The patterns of glucose-stimulated insulin secretion of perfused islets from control and mld-STZ mice at days 6 and 12 after the first injection are shown in Fig. 1. At day 6, mld-STZ mice show a normal biphasic pattern, with a first phase lasting from minute 3 to minute 7, and the second phase lasting from minute 10 to minute 40. The insulin secretion patterns of mld-STZ mice evolved, and perfused islets from these animals at day 12 after the first injection showed a significant deterioration of the first and second phase of insulin secretion.

**DISCUSSION**

Although altered lipid metabolism is usually present with Type 1 diabetes, its role mainly in the early stages of the disease has not been extensively studied. The present work focuses on the function of lipids in the progression of Type 1 diabetes that was experimentally induced in C57BL/6J mice by the administration of mld-STZ. The study was performed before and after the onset of clear hyperglycemia, and the two major new findings follow.

First, 6 days after the first dose of streptozotocin, plasma FFA levels were significantly increased, whereas both glucose and insulin levels remained similar to those observed in the control group of mice injected with citrate buffer. At that time, a marked increase in triglyceride content within the gastrocnemius muscle was accompanied by both a diminished PDHc and increased PDH-kinase activities, suggesting an impaired glucose oxidation. Furthermore, a decrease of both triglyceride content and LPL activity was recorded in epididymal fat tissue.

Second, a more pronounced increase of FFA levels occurred after 12 days of the first injection of streptozotocin together with hypertriglycerideremia, hyperglycemia, and a significant reduction of plasma insulin level. Both the adipose tissue and the gastrocnemius muscle showed a further deterioration of all the parameters mentioned after 6 days. Moreover, in the gastrocnemius muscle, an impaired nonoxidative pathway of glucose metabolism was observed at this time point. Also, perfused islets of mice after 12 days of mld-STZ showed a significant reduction of the first and second phase of insulin secretion patterns under the stimulus of glucose. Furthermore, our laboratory’s previous results showed apoptosis and necrosis of the β-cell at this time, indicating that there has been a significant loss of mass (18). However, as in perfused isolated islets in which we compare groups of islets that have a good viability, these results suggest that pancreas from mld-STZ mice have not only reduced mass but also an impaired residual islet functional secretion.

Regarding plasma FFA levels, Kurtz et al. (21) recently observed in NOD mice (a genetic model of autoimmune Type 1 diabetes) a moderate increase of plasma FFA level in the prediabetic animal when both plasma glucose and insulin levels were within normal range. These findings are in agreement with our present results in the early stages of diabetes development. In the presence of hyperglycemia and moderate insulin deficiency (12 days after the first dose), we observed a further increase of plasma FFA and triglyceride levels. Similarly, Ebara et al. (10), using the same animal model, showed a significant increase of plasma triglyceride and cholesterol levels 4 wk after the first administration of mld-STZ, whereas Kunjathoor et al. (20) observed a moderate increase of plasma triglyceride in the same strain of mice after 24 wk of mld-STZ treatment. A significant increase of plasma FFA was observed by Kurtz et al. (21) in NOD mice in the presence of overt diabetes.
An oversupply of lipid could deteriorate insulin action in its target tissues (e.g., skeletal muscle). In C57BL/6J mice, at day 6 after the first streptozotocin injection, the present results show a substantial increase of triglyceride store within the gastrocnemius muscle that occurred concomitant with a significant reduction of the PDHc activity, a key enzyme in the control of glucose oxidation. A decreased flux through the PDHc is associated with lower active form of the PDHc and higher PDH-kinase levels, and the inhibition of this enzyme complex limits the oxidation of pyruvate derived from glycolysis (32). These, together with the observed increased of plasma FFA concentration, might be an early indication of the disturbance of lipid metabolism and/or fuel utilization in the face of basal normoglycemia. Both alloxan diabetic rats and rats with severe diabetes induced by high doses of streptozotocin also show a significant increase of muscle triglyceride concentration together with elevated FFA and reduced plasma insulin levels (32, 38). In this regard, a worsening of all the above parameters was recorded in the presence of hyperglycemia and insulopenia at day 12 after the first administration of mld-STZ. Moreover, in gastrocnemius muscle, both glycogen and G-6-P concentrations, as well as GSA, were significantly reduced at this time, indicating an impaired nonoxidative pathway of glucose metabolism. Also, Ebeling et al. (11) observed an increase of triglyceride concentration within the skeletal muscle of patients with IDDM.

Recently, in rats with moderate or severe Type 1 diabetes induced by streptozotocin injection, Luiken et al. (26) showed an increased fatty acid transport across the plasma membrane in heart and skeletal muscle that occurred with a concomitant increase in plasma membrane transporter FAT/CD36. At present, we are unaware of any studies examining the fatty acid transport before and after the development of hyperglycemia in Type 1 diabetes induced by mld-STZ. However, we cannot discard the possibility that an increased transport of plasma FFA in tissues (e.g., gastrocnemious muscle) could contribute to the enhancement of triglyceride content.

Adipose tissue is a target tissue to supply fatty acid for whole body utilization. Plasma FFA levels, which are affected by fat cell lipolysis, exert an important modulator effect on insulin action. Our results show a significant decrease of both the triglyceride content and the LPL activity in the epididymal fat tissue of mice with mld-STZ 6 days after the first dose. This is accompanied by elevated plasma FFA levels and normoglycemia. The rate-limiting step of adipose tissue lipolysis is the hydrolysis of triglyceride by hormone-sensitive lipase. Although the enzymatic activity of hormone-sensitive lipase in the adipose tissue was not performed in the present work, one possible explanation for the significant increase of plasma FFA could be that an accelerated lipolysis operates in this tissue at day 6 after the first streptozotocin injection and keeps on doing so in the presence of hyperglycemia. In this regard, in insulin-deficient diabetes induced in rats by a high dose of streptozotocin, an increase of both adipose tissue lipolysis and circulating FFA was observed (41). Moreover, adipocytes from animals with severe diabetes show a significant increase of both basal lipolysis and a sensitivity to lipolytic agents, as well as a resistance to the antilipolytic action of insulin (36). However, Lacasa et al. (22) observed that a reduced lipid content occurring in streptozotocin-treated rat adipocytes is probably the consequence of a defective lipogenesis due to reduced lipoprotein lipase activity and glucose uptake rather than an increased fat mobilization secondary to enhanced sensitivity of lipolysis to catecholamines. Because LPL activity was reduced in mld-STZ mice and we do not measure lipogenesis and glucose uptake, we cannot discard the possibility that defective lipogenesis could also contribute to a decrease of the triglycerides content within the adipocytes.

In the present work, no changes in both glucose and insulin levels were recorded after 6 days of the first mld-STZ injection. At the present time, we are unaware of any data that could help to explain these results. This was an unexpected finding, because a significant increase of plasma FFA was already observed at that time. However, we have recently observed that, under the intraperitoneal glucose tolerance test, mice with mld-STZ show a significant increase of the plasma glucose level that does not return to normal values at minute 120 of the test at day 7 after the first injection (data not shown). This finding may indicate early evidence of deterioration of the whole body peripheral insulin sensitivity or an insufficient insulin release that could contribute to the early alteration of lipid metabolism. Also, in previous work from our laboratory (18), we demonstrated that a moderate basal hyperglycemia appears in C57BL/6J mice with mld-STZ at day 9 after the first injection. This was accompanied by altered insulin secretion patterns from perfused isolated islets under the stimulus of glucose.

It is well known that, in the mld-STZ model, a direct toxic effect of streptozotocin and/or a subsequent autoimmune reaction leads to the deletion of β-cells (3, 29). In this regard, the possibility that mld-STZ could be acting through a direct toxic effect on pancreas should be considered. However, in a previous work using congenitally athymic mice injected with mld-STZ (1), the toxic effect of streptozotocin was not higher than 10%. O’Brien et al. (28) showed that apoptosis, the mode of cell death responsible for β-cell loss in C57BL/6 mice with mld-STZ, precedes the appearance of T cells in the islets and continues throughout the period of insulitis. They reported two peaks in the incidence of the β-cell apoptosis: at day 5, which corresponds to an increase of the blood glucose level, and at day 11 with lymphocytic infiltration in the islets (insulitis). Similar to the above results, our laboratory (18) observed an increase of apoptotic β-cells in C57BL/6J mice with mld-STZ as early as day 4 after the first dose of the diabetogenic drug, whereas insulitis was present at day 6.

Immune responses regulated by local cytokines may contribute to the diabetic state since reduction and upregulation of Th2-type cytokines were respectively associated with susceptibility and resistance to mld-STZ-induced diabetes (27). Recently, a possible synergy between cytokines and lipids in causing β-cell cytotoxicity has been inferred from results demonstrating that the toxicity of interleukin-1β is enhanced in triglyceride-rich islets and reduced in fat-depleted islets after caloric restriction, leptin, or troglitazone treatment in rats (33).

Finally, the present study suggests for the first time that, in mice with Type 1 diabetes induced by mld-STZ, an enhanced lipolysis of fat pad leads to an increase in the availability of plasma FFA, which seems to play a role in the early steps of diabetes evolution.
REFERENCES


