In Vivo Role of NAD(P)H:Quinone Oxidoreductase 1 (NQO1) in the Regulation of Intracellular Redox State and Accumulation of Abdominal Adipose Tissue*

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NAD(P)H:quinone oxidoreductase 1 (NQO1) is a flavoprotein that utilizes NAD(P)H as an electron donor, catalyzing the two-electron reduction and detoxification of quinones and their derivatives. NQO1--/-- mice deficient in NQO1 activity and protein were generated in our laboratory (Rajendiran, V., Joseph, P., Lee, Y. H., Kimura, S., Klein-Santo, A. J. P., Gonzalez, F. J., and Jaiswal, A. K. (1998) J. Biol. Chem. 273, 7382–7389). Mice lacking a functional NQO1 gene (NQO1--/--), nor NAD(P)H, NADH and NAD(P)H combined; HPLC, none acceptor oxidoreductase, quinone reductase; NQO2, a second cytosolic form of NAD(P)H:quinone oxidoreductase also known as DT diaphorase; NQO1+/+ mice. In the present report, we show that NQO1--/-- mice exhibit significantly lower levels of abdominal adipose tissue as compared with the wild-type mice. The NQO1+/+ mice showed lower blood levels of glucose, no change in insulin, and higher levels of triglycerides, β-hydroxybutyrate, pyruvate, lactate, and glucagon as compared with wild-type mice. Insulin tolerance test demonstrated that the NQO1--/-- mice are insulin resistant. The NQO1+/+ mice showed significantly higher levels of triglycerides, lactate, pyruvate, and glucose. The liver glycogen reserve was found decreased in NQO1+/+ mice as compared with wild-type mice. The livers and kidneys from NQO1+/+ mice also showed significantly lower levels of pyridine nucleotides but an increase in the reduced/oxidized NAD(P)H: NAD(P) ratio. These results suggested that loss of NQO1 activity alters the intracellular redox status by increasing the concentration of NAD(P)H. This leads to a reduction in pyridine nucleotide synthesis and reduced glucose and fatty acid metabolism. The alterations in metabolism due to redox changes result in a significant reduction in the amount of abdominal adipose tissue.

NAD(P)H:quinone oxidoreductase 1 (NQO1)^1 is a 274-amino acid flavoprotein that catalyzes the two-electron reduction and detoxification of quinones and their derivatives (1–3). The cytosolic NQO1 activities, purified from rat liver and human adipose tissue, have been characterized and cloned (1–3). NQO1 utilizes both NADH and NADPH as electron donors (1–3). The two-electron reduction of quinones does not result in the formation of free radicals (semiquinones) and highly reactive oxygen species, hence protecting cells against the adverse effects of quinones and their derivatives (1–3). As a protective agent, NQO1 activity has been shown to prevent the formation of highly reactive quinone metabolites (4), detoxify benz(a)pyrene quinone (5), and reduce chromium (VI) toxicity (6). Recently, NQO1 was also shown to reduce benzo(a)pyrene and benz(a)pyrene quinone induced mutagenicity (7, 8). NQO1 activity is present in all tissues but at different levels (1–3). Various investigators have observed large variations in NQO1 activity between individuals, in different tissues from the same individual, and between normal/tumor tissues (1–3). It is generally accepted that tumor tissues and cells of hepatic and colonic origin express higher levels of NQO1, as compared with normal tissues and cells of similar origins (1–3). The normal tissue that surrounds the hepatic tumors also expresses higher levels of the NQO1 gene, presumably to play an unknown role in tumor progression (9). NQO1 gene expression is induced in response to xenobiotics, antioxidants, oxidants, heavy metals, UV light, and ionizing radiation (1–3, 10). Interestingly, NQO1 is part of an electrophilic and/or oxidative stress-induced cellular defense mechanism that includes the induction of more than two dozen genes (1–3). The coordinated induction of these genes, including NQO1, presumably provides cellular protection against free radical damage, oxidative stress, and neoplasia.

Despite the large volume of knowledge about NQO1, the in vivo role of NQO1 remains unknown. To examine the in vivo role of NQO1, we used targeted gene disruption to generate NQO1+/-- mice (11). These mice are born normal and reproduce normally. However, the NQO1+/-- mice exhibited increased toxicity to menadione when compared with the wild-type mice. In the present study, we demonstrate that NQO1+/-- mice exhibit a significant reduction or absence of abdominal adipose tissue, as compared with the wild-type mice. We also demonstrate that several metabolic pathways are altered in NQO1+/-- mice as compared with wild-type mice. This was evident from lower blood levels of glucose and higher levels of triglycerides, β-hydroxybutyrate, lactate, pyruvate, and glucagon in NQO1+/-- mice as compared with wild-type mice. The NQO1+/-- mice showed lower levels of glycogen but higher levels of glucose, triglycerides, lactate, and pyruvate. We further demonstrate that NQO1+/-- mice are insulin resistant as compared with wild-type mice. In addition, the NQO1+/-- mice livers and kidneys showed decreased pyridine nucleotides but higher NAD(P)H:NAD(P) ratio as compared with wild-type mice. These results suggest that NQO1 plays a significant role in regulation of intracellular redox.
status and hence metabolic pathways leading to the accumulation of abdominal adipose tissue.

**EXPERIMENTAL PROCEDURES**

**Breeding of Wild-type and NQO1−/− Mice—** C57BL6 NQO1−/+ and wild-type mice were bred in our laboratory (11). The animals were housed in polycarbonate cages, maintained with a 12-h light/dark cycle, a temperature of 24 ± 2 °C, a relative humidity of 55 ± 10%, and a negative atmospheric pressure. The mice were fed standard rodent chow and acidified water ad libitum. Twenty-four-, 48-, and 72-wk-old male and female mice were used in the present studies. However, because of the similarity in the results the data are shown only for male mice. Animals received humane care throughout the experiment according to AALAC guidelines for animal welfare.

**Collection of Blood and Tissues for Analysis—** Mice were anesthetized by a brief exposure to isoflurane (VEDCO Inc., St. Joseph, MO). The mice were then given a 0.25-ml intraperitoneal injection of 50% urethane. Blood was extracted from the hearts with a 1-ml EDTA-coated syringe/22G1 needle and placed in Eppendorf tubes. The tubes were inverted several times to ensure uniform clotting. After a 20-min incubation at room temperature, the tubes were centrifuged at 14,000 rpm for 20 min. The serum was withdrawn from the tubes and frozen at −20 °C until analysis. Blood and tissue samples were taken at the same time of the day. In related experiments, animals were fasted for 16 h and blood was drawn for analysis as described earlier.

**Serum Analysis—** The glucose and triglyceride levels were analyzed in the serum samples using a Cobas Mira System and Sigma reagents. β-Hydroxybutyrate, lactate, and pyruvate levels were measured using Sigma Diagnostic Kits and protocol supplied by the manufacturer. Linco Research Inc. (St. Charles, MO) using a sensitive radioimmunoassay kit for the determination of concentration of glucagon and insulin in the serum.

**Insulin Tolerance Test—** The insulin tolerance test was performed by previously described method (12). Seventy-two-week-old wild-type and age-matched NQO1−/− mice were used. The mice were fasted for 16 h but given water ad libitum. Insulin (0.15 IU/kg body weight) was administered by intraperitoneal injection of insulin to the fasted mice. The blood was drawn by retro-orbital bleeding and analyzed for blood glucose using the Accu Chek kit (Roche Molecular Biochemicals).

**NQO1 Activity and Western Blot Analysis—** The various tissues (liver and kidney) from 24-week-old wild-type and NQO1−/− mice were homogenized in 50 mM Tris (pH 7.4) containing 0.25 M sucrose. This removes any residual DNA/protein and also serves as a filter in the serum. Glucose and triglyceride levels were analyzed in the serum samples using a Cobas Mira System and Sigma reagents. β-Hydroxybutyrate, lactate, and pyruvate levels were measured using Sigma Diagnostic Kits and protocol supplied by the manufacturer. Linco Research Inc. (St. Charles, MO) using a sensitive radioimmunoassay kit for the determination of concentration of glucagon and insulin in the serum.

**Measurement of Pyridine Nucleotides in Tissues—** The liver and kidney tissues collected by classical and freeze-clamping methods were homogenized in chilled buffer containing 200 mM KCN, 1 mM bathophenanthroline, and 60 mM ROH using a Potter-Elvejhem homogenizer system. The pyridines were extracted and analyzed by these procedures by procedures as previously described (15). Briefly, the homogenate was extracted rapidly with chloroform several times until minimal precipitate was observed at the interface of the buffer and chloroform. The supernatant was then passed through a 0.45-µm Ultrafree-MC filtration device (Millipore) by centrifuging at 5000 rpm for 10 min at 4 °C. This removes any residual DNA/protein and also serves as a filter before the samples are loaded onto the HPLC column. The various pyridine nucleotides (NAD, NADP, NADPH, and NADPDH) were separated, analyzed, and quantitated using a C18 chromatography column (Waters) and HPLC (Waters). The mobile phase consisted of 50 mM potassium phosphate buffer (pH 7.05)/acetonitrile (97:3) as suggested by the manufacturer. The Rp values of the NAD, NADP, NADPH, and NADPDH standards were calculated and employed for quantification of the pyridine nucleotides in the various samples under identical conditions. The classical and freeze-clamping techniques yielded quite similar results. Therefore, the values from both these methods were combined.

**RESULTS**

Wild-type (NQO1+/+) and NQO1−/− mice were analyzed for NQO1 activity and protein levels (Fig. 1). The highest amount of NQO1 activity was observed in the kidney, followed by the liver and abdominal adipose tissue. The NQO1 activities were similar for male and female mice, therefore, the data has been combined. NQO1 activity was not detected in the kidney or abdominal adipose tissue from NQO1−− mice. However, the livers from NQO1−−/− mice contained a small amount (<15% of wild type) of NQO1 activity. Western blot analysis did not detect any NQO1 protein in these three tissues (liver, kidney, and abdominal adipose), but did detect NQO1 protein in similar tissues from wild-type (NQO1+/+) mice. The small amount of NQO1 activity detected in the liver of NQO1−/− mice may be due to an isoenzymic form of NQO1, since the NQO1 protein was not detected in Western analysis of NQO1−/− liver tissue (Fig. 1). A comparison of total body weight of wild-type and NQO1−/− mice was performed. The results indicated that NQO1−/− mice were significantly lighter in weight as compared with wild-type mice at all the three (24, 48, and 72 weeks old) ages of mice studied (Table I).
The results of the analysis of the abdominal adipose tissue in 24-, 48-, and 72-week-old wild-type and NQO1-/- mice are shown in Fig. 2. The amount of abdominal adipose tissue increased with age in the wild-type mice. In contrast to the wild-type mice, the NQO1-/- mice did not accumulate abdominal adipose tissue with age. This resulted in a significant reduction of abdominal adipose tissue in NQO1-/- mice, especially in the older animals. The 24- and 48-week-old NQO1-/- mice showed a 20 and 38% reduction in abdominal adipose tissue, as compared with age-matched wild-type controls. The most significant (p < 0.001) reduction in adipose tissue, between wild-type and NQO1-/- mice, was observed in 72-week-old mice (Figs. 2 and 3). They showed a 326% reduction in abdominal adipose tissue, as compared with age-matched wild-type mice.

Serum glucose levels of 24-, 48-, and 72-week-old wild-type and NQO1-/- mice are shown in Table II. Serum glucose decreased by 11% (p < 0.1), 35% (p < 0.01), and 36% (p < 0.001) in 24-, 48-, and 72-week-old NQO1-/- mice, when compared with the age matched wild-type mice (Table II). An increase in the pyruvate (37%, p < 0.01), lactate (18%, p < 0.05), triglycerides (18%, p < 0.05), and β-hydroxybutyrate (48%, p < 0.007) contents were observed in the serum of 72-week-old NQO1-/- mice over the age-matched controls (Table II). Similar results were also observed with mice fasted for 16 h. The concentration of serum glucose decreased by 20% (p < 0.01) and triglycerides showed an increase by 22% (p < 0.05) in the 72-week-old NQO1-/- mice as compared with the age-matched wild-type mice. These changes were more or less similar to that observed when mice were fed ad libitum. However, the serum β-hydroxybutyrate levels showed significantly higher differences in fasted mice as compared with mice fed ad libitum. The NQO1-/- mice showed a 69% increase (p < 0.005) in the 72-week-old NQO1-/- when compared with the wild-type mice after 16 h of fasting (Table II). The NQO1-/- mice also demonstrated a marked increase in the concentration of metabolites such as glucose (105%, p < 0.01), lactate (48%, p < 0.005), pyruvate (79%, p < 0.005), and triglycerides (180% p < 0.005) as compared with wild-type mice (Table III). However, liver glycogen reserve of NQO-/- mice was decreased by 27% (p < 0.025) as compared with the wild-type mice (Table III). Among the hormones that regulate metabolism, no significant alterations were observed in blood-insulin concentrations between NQO1-/- and wild-type mice (Table IV). However, gluca gon levels exhibited a 30% increase (p < 0.05) in the NQO1-/- mice as compared with wild-type mice (Table IV). The insulin tolerance test in the 16-h fasted wild-type mice showed that the blood glucose levels in these mice decreased by about 18, 28, and 32% in 20, 40, and 60 min, respectively, after insulin was administered to the animals. In the NQO1-/- mice the decrease of blood glucose was 6, 9, and 17% at 20 min, 40 and 60 min after administration of insulin (Table V).

The amounts of NAD, NADP, NADH, and NADPH and the ratios of NADH/NAD and NADPH/NADP in the liver and kid-

### Table I

| Age (weeks) | Body weight (g) * | *Mean ± S.D. of 10 mice. The significance p values are shown in parentheses.|
|------------|------------------|--------------------------------------------------------------------------|
| 24         | Wild-type        | 29.1 ± 1.2                                                                |
|            | NQO1-/-          | 25.4 ± 1.8 (0.005)                                                        |
| 48         | Wild-type        | 28.7 ± 1.1                                                                |
|            | NQO1-/-          | 25.6 ± 4.6 (0.05)                                                         |
| 72         | Wild-type        | 33.9 ± 4.1                                                                |
|            | NQO1-/-          | 30.9 ± 3.1 (0.025)                                                        |

*Mean ± S.D. of 10 mice. The significance p values are shown in parentheses.

## Discussion

The NAD(P)H:quinone oxidoreductases are enzymes that are present in all tissues (1–3). In humans, genetic evidence indicates that different forms of NQOs are encoded by four gene loci (1–3). Two of these gene loci (NQO1 and NQO2) encode proteins that constitute ~85% of the total cellular NQO activity (1). Among all the NQOs known so far, cytosolic NQO1 is highly abundant and is the most extensively studied enzyme (1). In the present report, NQO1-/- mice were used to examine the in vivo role of NQO1.

NQO1-/- mice showed significant decreases in total body weight and abdominal adipose tissue, as compared with the wild-type mice. The decrease in abdominal adipose tissue was more significant in older mice than younger mice. This obvious difference in older (72 weeks) animals was due to accumulation of abdominal adipose tissue in the wild-type mice and lower (or no) accumulation of adipose tissue in the aging NQO1-/-
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FIG. 3. Abdominal adipose tissue in 72-week-old wild-type and NQO1−/− mice.

WILD-TYPE

NQO1−/−

TABLE II
Concentration of various metabolites in serum of wild-type and NQO1−/− mice (mg/dL)

Mean ± S.D. of six mice. The significance p values are shown in parentheses.

| Metabolite    | Wild-type (mg/dL) | NQO1−/− (mg/dL) | p       |
|---------------|-------------------|-----------------|---------|
| Glucose       | 271 ± 37          | 241 ± 16 (0.1)  | 0.10    |
| Pyruvate      | 2.35 ± 0.297      | 2.85 ± 0.313 (0.05) | 0.01    |
| Lactate       | 28.5 ± 3.91       | 53 ± 8          | 0.004   |
| Triglycerides | 3.91 55 ± 8       | 7.20 ± 2.0 (0.01) | 0.015   |
| β-Hydroxybutyrate | 1.98 ± 0.62 | 2.90 ± 0.20 (0.01) | 0.015   |

Metabolite levels in livers of 48-week-old wild-type and NQO1−/− mice

Data are mean ± S.D. of six mice. The significance p values are shown in parentheses.

| Metabolite | Wild-type (mg/g) | NQO1−/− (mg/g) | p       |
|------------|------------------|----------------|---------|
| Glucose    | 5.8 ± 0.4        | 11.9 ± 3.7 (0.01) | 0.10    |
| Glycogen   | 139.5 ± 27.9     | 101.9 ± 18.2 (0.025) | 0.01    |
| Lactate    | 5.9 ± 0.5        | 8.7 ± 1.0 (0.005) | 0.004   |
| Pyruvate   | 42.0 ± 6.9       | 75.3 ± 13.4 (0.005) | 0.01    |
| Triglycerides | 0.5 ± 0.1 | 1.4 ± 0.3 (0.005) | 0.01    |

TABLE III
Metabolite levels in livers of 48-week-old wild-type and NQO1−/− mice

Data are mean ± S.D. of six mice. The significance p values are shown in parentheses.

Insulin tolerance test in wild-type and NQO1−/− mice

Values expressed as percent decrease in blood glucose concentration after insulin administration from the fasting glucose levels. Values are mean ± S.D. of five mice. The significance p values are shown in parentheses.

| Time (min) | Wild-type | NQO1−/− |
|------------|-----------|---------|
| 20         | 18.3 ± 0.51 | 6.3 ± 0.5 (0.005) |
| 40         | 28.3 ± 12.6 | 9.1 ± 1.9 (0.01) |
| 60         | 32.1 ± 0.66 | 16.6 ± 4.2 (0.005) |

TABLE IV
Serum levels of insulin and glucagon in 48-week-old wild-type and NQO1−/− mice

Data are mean ± S.D. of six mice. The significance p values are shown in parentheses.

| Hormone   | Wild-type | NQO1−/− |
|-----------|-----------|---------|
| Insulin (microunits/ml) | 1.10 ± 0.244 | 1.03 ± 0.245 (NS) |
| Glucagon (ng/ml)         | 0.10 ± 0.004 | 0.14 ± 0.015 (0.05) |

mice. The possible reasons for the decreased abdominal adipose tissue may be inefficient fat synthesis, ineffective fat deposition, and/or degradation of adipose tissue.

A decrease in blood glucose and increase in blood and liver lactic and pyruvic acid indicated that glucose (gluconeogenesis) and possibly fatty acid synthesis are decreased in NQO1−/− mice as compared with wild-type mice. The lactic and pyruvic acid are two key substrates for gluconeogenesis, a metabolic pathway to synthesize glucose (20). Their accumulation in blood and liver strongly indicated that glucose synthesis is down-regulated in NQO1−/− mice (20). The lower levels of blood glucose and higher levels of serum glucagon in NQO1−/− mice presumably stimulated glycogenolysis in the livers of NQO1−/− mice leading to increased production of glucose due to breakdown of glycogen to meet with the energy requirements of the liver. This is supported by an increase in glucose and decrease in glycogen of liver in NQO1−/− mice as compared with wild-type mice. The increase in glucagon is also known to stimulate gluconeogenesis (21). However, this may not be the case in NQO1−/− mice that demonstrated accumulation of pyruvate and lactate in liver, two substrates for gluconeogenesis. Therefore, it is likely that most of the glucose in the liver came from the breakdown of glycogen reserves rather than gluconeogenesis. It is surprising though that there is sufficient glucose in the liver, yet the serum glucose is low and the circulating insulin concentration is also unchanged in
NQO1−/− mice. It is possible that NQO1−/− mice liver requires glucose as its major energy source due to down-regulation of other metabolic processes leading to increased requirement of glucose in the livers of NQO1−/− mice. However, the possibility of inefficient glucose transport from the liver in NQO1−/− mice cannot be ruled out.

The insulin tolerance test demonstrated that NQO1−/− mice are insulin resistant as compared with the wild-type mice. However, the insulin resistance did not appear to be of severe form as observed in the case of lipodystrophic mice (22). We believe that high triglyceride content in the peripheral blood of the NQO1−/− mice is one of the factors causing insulin resistance in NQO1−/− mice.

The increase in serum and liver triglycerides in NQO1−/− mice when compared with wild-type mice may suggest that the breakdown of accumulated fat also contributed to lower abdominal adipose tissue in the NQO1−/− mice. An increase in β-hydroxybutyrate in NQO1−/− mice also supported breakdown of adipose tissue. It is known that β-hydroxybutyrate is synthesized from fatty acids generated after the breakdown of adipose tissue and serves as an alternative source of energy in tissues like brain (20, 23). The hypoglycemic condition in NQO1−/− mice presumably activated alternative pathways of energy generation in NQO1−/− mice that led to increase in β-hydroxybutyrate production. At this time, however, the role of inefficient dietary fat deposition in the adipocytes of NQO1−/− mice in addition to down-regulation of glucose and fat synthesis and increased fat breakdown remains unknown.

The studies on metabolic precursors and substrates have provided sufficient evidence that glucose and fat metabolic pathways are altered in NQO1−/− mice as compared with wild-type mice. It is known that a physiologically favorable equilibrium between the reduced and oxidized forms of NAD(P) is crucial for many of the enzymatic reactions that catalyze reactions leading to the synthesis of pyridine nucleotides, glucose, and adipose tissue (20). Any alteration in the intracellular levels of NAD(P)H and NAD(P) is known to affect the pentose phosphate pathway that generates pentoses for synthesis of pyridine nucleotides, gluconeogenesis, and fatty acid metabolism (20). In the present studies, NQO1−/− mice showed decreased pyridine nucleotide levels but higher ratios of NADPH:NAD and NADH:NAD. NQO1 is known to utilize NAD(P)H as an electron donor, which generates NAD(P) (1–3). Therefore, the loss of NQO1 in NQO1−/− mice resulted in the accumulation of NAD(P)H and alterations in the intracellular redox status. The accumulation of NAD(P)H presumably inhibited the pentose phosphate pathway leading to lower levels of pyridine nucleotides in NQO1−/− mice, as compared with wild-type mice. The lower levels of pyridine nucleotides may have contributed to the decrease in gluconeogenesis and fatty acid metabolism (20). Therefore, an altered intracellular redox state, caused by higher ratios of NAD(P)H:NAD(P) may be a major factor that contributed to the down-regulation of gluconeogenesis and adipose synthesis in NQO1−/− mice.
These results raise an interesting question regarding the endogenous substrate(s) for NQO1, utilizing NAD(P)H. Earlier studies have suggested that NQO1 reduces CoQ and protects membranes from oxidative damage (24). There may be other cellular molecules that serve as substrates for NQO1 but remain unknown. There are several proteins that contain nitrotyrosines (25) and many proteins contain quinones as cofactors (26). It is possible that NQO1 catalyzes the reduction of nitrotyrosines or quinone cofactors, thus affecting the structure, function, and/or stability of these proteins. Future experiments should reveal more information on the endogenous substrates for NQO1. The possibility that NQO1 participates in pathways such as the citric acid and pentose phosphate pathways, as shown for the bacterial malate oxidoreductase, cannot be ruled out (27).

A model is depicted in Fig. 4 to describe the role of NQO1 in the regulation of intracellular redox status and gluconeogenesis. NQO1 utilizes NAD(P)H as an electron donor and catalyzes the two-electron reduction of known/unknown endogenous substances and quinones (1–3). This reaction generates oxidized NAD(P), which maintains a balance between NAD(P)/H and NAD(P). This balance, between the reduced and oxidized form of NAD(P), contributes to the intracellular redox status that is optimal for pyridine nucleotides, glucose synthesis, and fatty acid metabolism. Excess glucose and fatty acids, through metabolic pathways, are converted to triglycerides that accumulate in the abdominal adipose tissue. Disruption of the NQO1 gene leads to the loss of NQO1 protein, a decrease in the concentration of all pyridines (NAD, NADH, NADP, and NADPH) and accumulation of NADH and NADPH. This leads to an increased intracellular NAD(P)/H:NAD(P) ratio that results in an altered intracellular redox status. These changes decrease pyridine nucleotide synthesis, gluconeogenesis, and fatty acid metabolism, resulting in lower quantities of abdominal adipose tissue. The lower blood glucose levels may also stimulate degradation of accumulated adipose tissues to meet the demands of various tissues, including the brain.

In conclusion, we have demonstrated that NQO1 plays an important role in regulating the intracellular redox levels by oxidizing NAD(P)H. The loss of NQO1 leads to alterations in pyridine and intracellular redox status. This decreases gluconeogenesis, fatty acid metabolism, and significantly reduces the amount of abdominal adipose tissue.

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