HDQ (1-Hydroxy-2-dodecyl-4(1H)quinolone), a High Affinity Inhibitor for Mitochondrial Alternative NADH Dehydrogenase

EVIDENCE FOR A PING-PONG MECHANISM*"§

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Alternative NADH dehydrogenases (NADH:ubiquinone oxidoreductases) are single subunit respiratory chain enzymes found in plant and fungal mitochondria and in many bacteria. It is unclear how these peripheral membrane proteins interact with their hydrophobic substrate ubiquinone. Known inhibitors of alternative NADH dehydrogenases bind with rather low affinities.

We have identified 1-hydroxy-2-dodecyl-4(1H)quinolone as a high affinity inhibitor of alternative NADH dehydrogenase from Yarrowia lipolytica. Using this compound, we have analyzed the bisubstrate and inhibition steady-state kinetics. This suggests that there are no specific protein interaction partners for its membrane association. It remains unclear how the largely hydrophobic enzyme interacts with its highly hydrophobic substrate, ubiquinone. NADH, the other substrate of alternative NADH dehydrogenases, is highly hydrophilic.

Inspection of the YLNDH2 sequence revealed two βαβ-dinucleotide-binding domains that consist of two parallel β-strands connected by an α-helix (5). The sequence GXXGXXG, which marks the connection between the first β-strand and the connecting α-helix, makes close contact with the diphasope moiety of dinucleotide substrates or cofactors. The end of the second β-strand is often occupied by an acidic residue, which forms hydrogen bonds to the 2′ and 3′-hydroxyl groups of the adenine ribose (15). In the amino-terminal dinucleotide fold of Y. lipolytica NDH2, the acidic residue is replaced by serine. It has been suggested that this motif binds FAD (8). This proposal is consistent with the position of the FAD cofactor in the crystal structure of two different homologous lipoamide dehydrogenases (16, 17).

In the Escherichia coli sequence, a patch of highly basic amino acids that may contribute to membrane attachment by electrostatic interactions is found downstream of the GXXGXXG motif at positions 30–35. This pattern is missing at the corresponding position in Y. lipolytica NDH2, but the clustering of basic amino acids is observed immediately upstream of this motif. Two conserved regions almost exclusively consisting of apolar and aromatic residues have been proposed to form a possible interaction site for the hydrophobic substrate ubiquinone (5). However, no evidence is available that would experimentally identify the domains forming a binding pocket for the hydrophobic substrate ubiquinone.

Here we have characterized HDQ (1-hydroxy-2-dodecyl-4(1H)quinolone) as a novel high affinity inhibitor of membrane-bound NDH2 from Y. lipolytica and analyzed the mechanism of alternative NADH:ubiquinone oxidoreductases by bisubstrate and inhibition steady-state kinetics.

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Saccharomyces cerevisiae, for example, two external (SCNDE1 and SCNDE2) and one internal (SCNDI1) alternative NADH dehydrogenases are found (13). The obligate aerobic yeast Yarrowia lipolytica has only a single external alternative enzyme, YLNDH2 (5). It has been demonstrated that this external enzyme can be transformed into an internal version simply by adding a targeting signal for the mitochondrial matrix (14). This suggests that there are no specific protein interaction partners for its membrane association. It remains unclear how the largely hydrophobic enzyme interacts with its highly hydrophobic substrate, ubiquinone. NADH, the other substrate of alternative NADH dehydrogenases, is highly hydrophilic.

Alternative NADH dehydrogenases (NADH:ubiquinone oxidoreductases) are respiratory chain enzymes that carry out the same redox reaction as mitochondrial complex I. However, unlike this complicated multi-subunit enzyme, they do not contribute to the proton gradient across the respiratory membrane and are insensitive to complex I inhibitors like rotenone and piericidin A (for an overview see Ref. 1). Alternative NADH dehydrogenases are inhibited by flavones in the micromolar range. Acridones have been demonstrated to inhibit both complex I and alternative enzymes (2).

Alternative NADH dehydrogenases are found in respiratory chains of plants (3), fungi (4–7), many eubacteria (8, 9), and archaea (10–12). They consist of a single polypeptide chain that exhibits no obvious transmembrane domains and contains one molecule of FAD with the exception of the archaeenal enzymes that, presumably as an adaptation to thermic habitats, carry covalently attached FMN instead. Two conserved regions almost exclusively consisting of apolar and aromatic residues have been proposed to form a possible interaction site for the hydrophobic substrate ubiquinone (5). However, no evidence is available that would experimentally identify the domains forming a binding pocket for the hydrophobic substrate ubiquinone.

We have identified 1-hydroxy-2-dodecyl-4(1H)quinolone as a high affinity inhibitor of alternative NADH dehydrogenase from Yarrowia lipolytica. Using this compound, we have analyzed the bisubstrate and inhibition steady-state kinetics. This suggests that NADH and the ubiquinone headgroup interact with the same binding pocket in an alternating fashion.
HDQ Inhibits Y. lipolytica Alternative NADH Dehydrogenase

### MATERIALS AND METHODS

**Strains and Growth of Cells—** *Y. lipolytica* strain PIPO (NUGM-H2, *lys11–23, ura3–302, leu2–270, xpr2–322, MatA (18)) was used for studies on the reaction mechanism. Complex I deletion strain *nuamΔpUB7* (nuam::URA3, his-1, leu2–270, xpr2–322, NDH2 (14)) and NDH2 deletion strain GB 5.2 (*ndh2::URA3, his-1, leu2–270, xpr2–322, MatB) were used for characterization of the inhibitor HDQ. *Y. lipolytica* cells were grown in complete medium (1% yeast extract, 2% peptone) with 2% glucose at 27 °C.

**Preparation of Mitochondrial Membranes and Kinetic Measurements—** 5–10 g of cells were vortexed 13 x 1 min in 10 ml of ice-cold 600 mM sucrose, 20 mM Na+/Mops, pH 7.2, 1 mM EDTA, and 2 mM PMSF and 10 g of glass beads. After washing the glass beads with the same buffer, unbroken cells and cell fragments were sedimented at 2000 x g for 30 min. The supernatant was centrifuged again at 25,000 x g for 1 h to pellet mitochondrial membranes that were homogenized in a Potter-Elvehjem homogenizer, shock-frozen, and stored at −80 °C.

The steady-state NADH:DBQ oxidoreductase activity of membranes was measured as NADH oxidation at 340–400 nm (ε = 6.22 mm⁻¹ cm⁻¹) or 366–400 nm (ε = 3.3 mm⁻¹ cm⁻¹). The concentration of HDQ was measured at 329 nm (ε₂₃₂ = 9.4 mm⁻¹ cm⁻¹). To discriminate between NADH dehydrogenase activities in *Y. lipolytica* mitochondrial membranes, alternative dehydrogenase was measured in the presence of the complex I inhibitor DQA (2 μM) or using the complex I deletion strain *nuamΔpUB7*. Complex I activity was determined using dNADH as electron donor, which is oxidized specifically by complex I (19) or NADH with the NDH2 deletion strain GB 5.2. Tests were carried out at 30 °C in 20 mM Na+/Mops, 50 mM NaCl, and 2 mM KCN either in a stirred cuvette using a Photodiode array spectrophotometer (MultiSpec 1501, Shimadzu) or in a microtiter plate using a Microplate spectrophotometer (SPEKTRAmax® PLUS®345, Molecular Devices). The application of the Michaelis-Menten equation to enzymatic reactions involving highly hydrophobic substrates like ubiquinone in the presence of a membrane phase requires careful analysis of the primary data. In the case of alternative NADH dehydrogenase, we observed a non-linear dependence of the catalytic rate at low substrate concentrations. The data could not be fitted to either the standard Michaelis-Menten or to the Hill equation. Apparently, low concentrations of substrate were not available for reaction with alternative NADH dehydrogenase. The exact reason for this anomaly remained unclear. To deal with this experimental problem, we assumed that the substrate concentration [S] relevant for the rate v of alternative NADH dehydrogenase had to be corrected by an offset (in the range from 0 to 5 μM) that had to be determined for every data set. We corrected the added substrate concentration [S] added by this offset value c to obtain [S] as the substrate concentration available for binding and catalysis as shown in Equation 1.

\[
[S] = [S]_{\text{added}} - c
\]  

(Eq. 1)  

When we applied this correction, the experimental data were described very well by standard steady state kinetic equations. Michaelis-Menten parameters and the offset value c were determined by direct fit using the ENZFITTER software package (Biosoft).

### RESULTS

**Reactivity of NDH2 with Different Electron Acceptors—** We measured electron transfer rates with different electron acceptors to test the substrate specificity of alternative NADH dehydrogenase from *Y. lipolytica*. The activities were measured in the presence of 150 μM NADH and 60 μM of the respective

### Table 1

| Acceptor | Activity (μmol min⁻¹ mg⁻¹) | % | % Inhibition |
|----------|---------------------------|---|-------------|
| DBQ      | 1.4 ± 0.3                 | 100| 82 ± 3      |
| Ubiquinone-1 | 2.1 ± 0.4               | 152 ± 4| 79 ± 2      |
| Duroquinone | 0.7 ± 0.2                | 53 ± 8 | 23 ± 13     |
| Menadione | 0.7 ± 0.2                | 53 ± 5 | No inhibition |
| Dichlorophenol-indophenol | 1.5 ± 0.3 | 111 ± 5 | 15 ± 3  |

**FIG. 1.** Structure of HDQ.

**FIG. 2.** HDQ is a potent inhibitor of YLNDH2. The concentration of 1-hydroxy-2-dodecyl-4(1H)quinolone required for half-maximal inhibition (IC₅₀) of YLNDH2 was determined at a concentration of 30 μg/ml protein in the presence of 60 μM DBQ and 100 μM NADH. To selectively assay YLNDH2 activity, membranes of strain *nuamΔpUB7* were used (IC₅₀ = 200 μM). Insert, to selectively assay complex I activity, membranes of strain GB 5.2 were used (IC₅₀ = 2 μM).

**FIG. 3.** YLNDH2 employs a ping pong reaction mechanism. Hanes plots ([S]/v over [S]) of steady-state kinetics with mitochondrial membranes of wild type strain PIPO (20 μg/ml total protein in each assay) are shown. Vₘₐₓ and apparent Kₘ values for DBQ in the presence of five different concentrations of NADH were obtained from direct fits to the Michaelis-Menten equation and used to calculate the lines. NADH concentrations were 10 (●), 20 (□), 30 (○), 50 (◇), and 100 μM (▲). Vₘₐₓ values were 0.32 ± 0.02 (●), 0.60 ± 0.03 (□), 0.67 ± 0.02 (○), 0.94 ± 0.02 (◇), and 1.11 ± 0.02 unit/mg (▲). Apparent Kₘ values for DBQ were 1.3 ± 0.4 (●), 3.0 ± 0.7 (□), 3.9 ± 0.6 (○), 5.5 ± 0.6 (◇), and 7.4 ± 0.7 μM (▲). Each data point represents the mean ± S.D. of three independent measurements.

*Hanes plots ([S]/v over [S]) of steady-state kinetics with mitochondrial membranes of wild type strain PIPO (20 μg/ml total protein in each assay) are shown. Vₘₐₓ and apparent Kₘ values for DBQ in the presence of five different concentrations of NADH were obtained from direct fits to the Michaelis-Menten equation and used to calculate the lines. NADH concentrations were 10 (●), 20 (□), 30 (○), 50 (◇), and 100 μM (▲). Vₘₐₓ values were 0.32 ± 0.02 (●), 0.60 ± 0.03 (□), 0.67 ± 0.02 (○), 0.94 ± 0.02 (◇), and 1.11 ± 0.02 unit/mg (▲). Apparent Kₘ values for DBQ were 1.3 ± 0.4 (●), 3.0 ± 0.7 (□), 3.9 ± 0.6 (○), 5.5 ± 0.6 (◇), and 7.4 ± 0.7 μM (▲). Each data point represents the mean ± S.D. of three independent measurements.*
electron acceptor in four different preparations at a membrane concentration of 20 μg/ml (Table I). A rather high variability of the absolute specific activities seemed to reflect some variability in the quality of the mitochondrial membranes and possibly also variable expression levels of YLNDH2. However, relative to DBQ, the activities with the different electron acceptors were very similar in all of the preparations. Remarkably, the highest rates were obtained with hydrophilic ubiquinone-1 and not with DBQ, which with respect to its hydrophobicity came closest to the physiologically substrate ubiquinone-9. Somewhat lower electron transfer rates were observed with duroquinone and bicyclic menadione. The artificial electron acceptor dichloro-rophenol-indophenol, which is known to accept electrons from many NADH-dependent dehydrogenases, also gave catalytic activities that were even higher than with DBQ.

**HDQ Is a Potent Inhibitor of YLNDH2**—In a search for potent inhibitors of alternative NADH dehydrogenase, we tested the inhibitory effect of HDQ (Fig. 1) on the NADH:ubiquinone oxidoreductase activity of Y. lipolytica mitochondrial membranes from strain nuam/X/pUB 7 that lacks complex I. With DBQ as a substrate, 80–90% YLNDH2 activity was inhibited by 10 μM HDQ. Ubiquinone-1 reductase was inhibited to the same extent, but the inhibitor had no or only minor effects on the reduction rates of the other electron acceptors tested (Table I). Using the same assay with increasing inhibitor concentrations, we determined the HDQ concentration required for half-maximal inhibition of alternative NADH:ubiquinone oxidoreductase activity (IC50) as 200 nM (Fig. 2). HDQ was found to also inhibit complex I decylubiquinone reductase activity in membranes from strain GB 5.2 lacking YLNDH2. However, at an IC50 of 2 μM, it acted ten times less efficiently on this enzyme (Fig. 2, insert).

**YLNDH2 Bisubstrate Kinetics Suggest a Ping-Pong Reaction Mechanism**—To determine the kinetic mechanism for NADH:DBQ oxidoreductase activity, we measured a series of bisubstrate kinetics of alternative NADH dehydrogenase. Mitochondrial membranes from strain PIPO in the presence of 2 mg/ml (u)NADH (Equation 5) and

\[
V = \frac{V_{\text{max}}[\text{NADH}][\text{Q}]}{K_m^\text{NADH} + K_m^\text{Q}[\text{Q}] + [\text{NADH}][\text{Q}]}
\]  

(Eq. 2)

Refined fitting of the experimental data (not shown) using this equation resulted in \( K_m \) values of 16.5 μM for NADH and 7.0 μM for DBQ.

**HDQ Exhibits Non-competitive Inhibition Kinetics for Both Substrates of YLNDH2**—To determine the inhibition mode of the quinolone derivative HDQ, we performed steady-state inhibition kinetics for both substrates of alternative NADH dehydrogenase, NADH and DBQ. Initial analysis of the data (not shown) clearly suggested non-competitive inhibition for both substrates with similar values for the two inhibition constants. This conclusion appeared counterintuitive, because one would have expected that the hydrophobic inhibitor HDQ would compete with the hydrophobic substrate DBQ for a similar domain on the enzyme. However, there is a case of bisubstrate kinetics for which the observed pattern is predicted, namely if an enzyme operates by a ping-pong mechanism and if the inhibitor blocks both the enzyme, in our case, oxidized YLNDH2 = E-FAD in Scheme 1, and the intermediate state, in our case reduced YLNDH2 = E-FADH2 in Scheme 1 (21). Kinetic calculations, as described in the following, demonstrated that our data are consistent with a model in which the inhibitor also interacts with a complex consisting of enzyme and one of its substrates, presumably NADH. This situation is described by Scheme 1, where \( E \) is the enzyme, \( I \) is the inhibitor, \( Q \) is the oxidized, and \( QH_2 \) is the reduced quinone. The rate equation describing this situation (21) is shown in Equation 3.

\[
v = \frac{V_{\text{max}}[\text{NADH}][\text{Q}]}{K_m^\text{NADH} + K_m^\text{Q}[\text{Q}] + [\text{NADH}][\text{Q}](1 + [I]/K_i)}
\]  

(Eq. 3)

When Equation 3 is inverted the following double-reciprocal form is obtained as shown in Equation 4.

\[
\frac{1}{v} = \frac{\frac{K_m^\text{NADH}}{V_{\text{max}}} + \frac{K_m^\text{Q}[\text{Q}]}{V_{\text{max}}[\text{Q}]} + \frac{[\text{NADH}][\text{Q}](1 + [I]/K_i)}{V_{\text{max}}}}{\frac{1}{V_{\text{max}}[\text{NADH}][\text{Q}]}}
\]  

(Eq. 4)

Fig. 4 shows the corresponding double-reciprocal plots for inhibition kinetics with both substrates. As evident from increasing slopes and the fact that the lines do not intercept on the ordinate, inhibition kinetics were non-competitive for both substrates. If [NADH] is kept constant, the slope \( m \) in the double-reciprocal plots is given by Equation 5,

\[
m = \frac{K_m^\text{Q}[\text{Q}]}{V_{\text{max}}[\text{Q}]} + \frac{K_m^\text{NADH}[\text{NADH}][\text{Q}]}{V_{\text{max}}[\text{NADH}][\text{Q}]} \times [I]
\]  

(Eq. 5)

and, as Equation 4 is symmetrical for [Q] and [NADH], if [Q] is kept constant by Equation 6.

\[
m = \frac{K_m^\text{NADH}[\text{NADH}][\text{Q}]}{V_{\text{max}}[\text{NADH}][\text{Q}]} + \frac{K_m^\text{Q}[\text{Q}]}{V_{\text{max}}[\text{Q}]} \times [I]
\]  

(Eq. 6)

The inhibition constants \( K_i \) and \( K_m \) can be derived directly from the \( x \) axis intercepts of the linear secondary plots \( m \) over \([I]\) (Fig. 5A). The resulting inhibition constants were \( K_i = 340 \text{ nM} \) (Equation 5) and \( K_m = 290 \text{ nM} \) (Equation 6). Thus, within experimental error, both dissociation constants are the same. Similarly, the inhibition constants can be derived from the \( y \) axis intercepts \( b \) of the double reciprocal plots (Fig. 4) as shown in Equations 7 and 8.

\[
b = \frac{1}{V_{\text{max}}[\text{NADH}]} + \frac{1}{V_{\text{max}}[\text{Q}]} \left( \frac{K_m^\text{NADH}}{[\text{NADH}]} + 1 \right) \times [I]
\]  

(Eq. 7)
Apparent inhibition directly gives the inhibition constant \( K_i \) over \( [Q] \) (Fig. 5). For Equation 7, the \( x \) axis intercept of the secondary plots \( b \) over \( [I] \) (Fig. 5B) directly gives the inhibition constant \( K_i \) as 380 nM. The mean dissociation constant for HDQ of 330 nM derived from all four secondary plots fits rather well to the directly obtained IC\(_{50}\) value of \(-200\) nM (cf. Fig. 2).

A simulation (see supplementary material) based on the above kinetic model reveals that the IC\(_{50}\) value is critically affected by the steady-state concentration of \( E-FADH_2 \) that in turn depends on the ratio of the catalytic constants for the reduction of FAD and reoxidation of FADH\(_2\), \( k_{cat}^{NADH} \) and \( k_{cat}^{Q} \). Using the parameters obtained from the kinetic analysis, it can be deduced that quinone reduction should be at least ten times faster than NADH reoxidation, which is likely to occur by hydride transfer.

**DISCUSSION**

With an IC\(_{50}\) of 200 nM, HDQ is the most potent inhibitor of alternative NADH dehydrogenase identified so far. At 95 \( \mu \)M, the IC\(_{50}\) of the commonly used inhibitor flavone is almost 500-fold higher (4). As a hydrophobic quinolone derivative, HDQ was likely to act as ubiquinone analogue in a competitive manner. However, steady-state inhibition kinetics of HDQ followed a classical non-competitive pattern for both substrates, NADH and the hydrophobic ubiquinone derivative DBQ. This unexpected result could be explained based on a ping-pong mechanism that was deduced independently from the bisubstrate kinetics of alternative NADH dehydrogenase. Our data are consistent with a model in which the inhibitor HDQ shows competitive inhibition with the hydrophobic substrate DBQ and classical non-competitive inhibition with the hydrophilic substrate NADH. It should be noted that our data would also be consistent with a model in which both substrates are inhibited in a non-competitive fashion. However, this seems unlikely considering the structure and physicochemical properties of HDQ and ubiquinone. Moreover, the central conclusion that alternative dehydrogenase operates by a ping-pong mechanism would hold also in this case.

Results obtained by classical Michaelis-Menten kinetics have to be interpreted with great caution if membrane-associated enzymes are analyzed that react with highly hydrophobic substrates, as is the case for alternative NADH dehydrogenase. However, the fact that direct measurement of the IC\(_{50}\) value, inhibition kinetics, and bisubstrate kinetics gave fully consist-
ent results strongly supported our conclusion that the reaction of alternative NADH dehydrogenase with NADH and ubiqui-
none operates by a ping-pong mechanism. A ping-pong mecha-
nism was also deduced from kinetic studies with partially
purified SCNDI1 (22). However, these authors used the artifi-
cial hydrophilic electron acceptor dichlorphenol-indophenol as
the second substrate. As indicated by the quinone analogue HDQ (Table I), no conclusions on the physiological reaction mechanism can be
drawn from this study.

The absence of a ternary complex of alternative NADH de-
hydrogenase, NADH, and ubiquinone implied by the ping-pong
mechanism can be interpreted in two ways. 1) Either there are
two independent binding sites that are linked by a very strong
anti-cooperative effect, or 2) both substrates bind competitively
to a common binding pocket of the enzyme. A strong anti-
cooperative effect of the required type is rarely found, and it
is hard to see why this would be required for the simple electron
transfer reaction catalyzed by alternative NADH dehydro-

However, mutually exclusive binding of hydrophilic NADH
and hydrophobic ubiquinone to a common binding pocket also
does not seem very likely at first sight. Although a definitive
answer cannot be given based on kinetic analysis, the observed
substrate specificity clearly favors the latter option. The reac-
tivity of alternative dehydrogenase with quinone-like com-

This proposal is in line with the x-ray structure of the analogous mammalian quinone reductase QR1 (23) that catalyzes electron transfer from NAD(P)H to
water soluble quinone-like compounds. Cocrystallization with
NADPH and duroquinone revealed that both substrates bind in
a similar fashion: The same side of the isoalloxazine ring of the
FAD cofactor is stacked on to the duroquinone or the nicotin-

amid ring of NADPH. In summary, we conclude that alter-
native NADH dehydrogenase is highly likely to contain a com-
mon binding pocket for NADH and the ubiquinone headgroup.

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