Kinetic modelling helps to understand oxidative stress caused by an antioxidant

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Trisomy21 (Down Syndrome)

- Three copies of chromosome 21
- First described 1866 by J. L. Down
- Genetic basis discovered 1959
- Prevalence ca. 1:800
- Mental retardation and characteristic facial features
- Overexpression of the ca. 250 genes of chromosome 21
- Genes with possible relevance for Down Syndrome: SOD, COL6A1, ETS2, CAF1A, CBS, DYRK, CRYA1, GART, IFNAR
Superoxide Dismutase

\[ \text{SOD} \quad \rightarrow \quad \text{H}_2\text{O}_2 \quad \rightarrow \quad \text{H}_2\text{O} \]

\[ \frac{d\text{O}_2^-}{dt} = k_1 - k_2 \cdot \text{SOD} \cdot \text{O}_2^- \]

\[ \frac{d\text{H}_2\text{O}_2}{dt} = k_2 \cdot \text{SOD} \cdot \text{O}_2^- - k_3 \cdot \text{cat} \cdot \text{H}_2\text{O}_2 \]

\[ \text{O}_{2,ss} = \frac{k_1}{k_2 \cdot \text{SOD}} \]

\[ \text{H}_{2\text{O}_2,ss} = \frac{k_1}{k_3 \cdot \text{cat}} \]
Negative Effects

- Increased lipid peroxidation in Trisomy21
- Increased lipid peroxidation in cell cultures
- Increased mortality in transgenic *D. melanogaster*
- Lipid peroxidation, diminished prostaglandin synthesis and serotonin uptake in transgenic mice.
- Bacteria overexpressing SOD showed increased paraquat sensitivity.
Explanations

- The reaction of $\text{H}_2\text{O}_2$ with CuZnSOD leads to hydroxyl radical generation.
- $\text{O}_2^*$ radicals might reduce membrane damage by acting as chain breakers.
Lipid Peroxidation Chain Reaction
The reaction of H$_2$O$_2$ with CuZnSOD leads to hydroxyl radical generation.

O$_2^*$- radicals might reduce membrane damage by acting as chain breakers.

SOD cycles between a reduced and oxidised state. At low O$_2^*$- levels the intermediates might interact with other redox partners and increase the superoxide reductase activity of SOD.
Reactions
\{ k_1 \rightarrow 6.6 \times 10^{-7}, \ k_2 \rightarrow 1.6 \times 10^9, \ k_3 \rightarrow 1.6 \times 10^9, \ k_4 \rightarrow 10^5, \ k_5 \rightarrow 2 \times 10^4, \ k_6 \rightarrow 1, \ k_7 \rightarrow 3.4 \times 10^7, \ k_9 \rightarrow 10^6, \ k_{10} \rightarrow 2000, \ k_{11} \rightarrow 5 \times 10^8, \ k_{12} \rightarrow 10^7 \times 10^{-5}, \ k_{13a} \rightarrow 8700 \times 10^{-6}, \ k_{13b} \rightarrow 8700 \times 10^{-6}, \ k_{17} \rightarrow 3 \times 10^8, \ k_{18} \rightarrow 14, \ k_{19} \rightarrow 8.8 \times 10^4, \ SOD \rightarrow 10^{-5}, \ cat \rightarrow 10^{-5}\}
Increasing SOR Activity

\[ k_{3b} = 10 \times k_{3a} \]
Increasing SOO Activity

\[ 10 \times k_3b = k_3a \]
SOO/SOR Results

- In principle the SOO/SOR idea works.
- However, it is not clear why in experiments SOR activity is always greater than SOO activity.
- Alternative redox partners have only been demonstrated for CuZnSOD, not MnSOD.
Membrane Damage Termination

- LOO* remains constant throughout the entire range.
- L* and LOOH increase for small SOD values, but are constant otherwise.
- Why are the concentrations of L* and LOO* not increasing with increasing SOD?
Simplified Modell

\[ O_{2,ss}^{*-} = \frac{k_1}{2k_2 + \text{SOD}} \]

\[ \text{LOO}_{ss}^* = \frac{k_2}{k_4} \]

\[ L_{ss}^* = \frac{k_2 \cdot k_{3b}}{k_3 \cdot k_4} + \frac{k_1 \cdot k_2}{k_3 \cdot (2k_2 + \text{SOD})} \]

- LOO* doesn’t change because it is completely independent of SOD and O_2^{*-}. If the concentration of O_2^{*-} changes, membrane damage initiation changes by the same factor as the termination (for a given k_4).
- Without the back reaction k_{3b}, levels of L* should decrease continously with increasing SOD, and this can be confirmed by disabling this reaction in the full modell.
- => Chain breaker idea does not work !!
Simulation with full model and SOO equal to SOR (no effect)
If there are alternative reaction pathways for the superoxide radical, increasing SOD channels more of the available \( \text{O}_2^\cdot^- \) into the \( \text{H}_2\text{O}_2 \) generating branch and can thus increase oxidative stress.

This principle is independent of the SOD type (CuZnSOD, MnSOD).

\( k_{10} \) does not only represent membrane damage, but ALL other reactions of \( \text{O}_2^\cdot^- \). Therefore \( k_{10} \) can be much larger than the value used in the modell and so the resulting effect on \( \text{H}_2\text{O}_2 \) can also be much larger.
Summary

- Overexpression of the antioxidant SOD leads to increased oxidative stress.
- We created a mathematical model to test some possible explanations.
- Only one proposed idea (SOD cycling) works as suggested under certain conditions.
- Studying the model we discovered an additional, more general, mechanism that might account for the increased oxidative stress.