Effect of ET\textsubscript{B} Receptor Agonist, IRL-1620, on Beta Amyloid (A\textbeta) Induced Oxidative Stress and Cognitive Impairment in Rats

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**Purpose**
Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by cerebrovascular and neuronal dysfunctions leading to a progressive decline in cognitive functions. Endothelin (ET) and its receptors have been considered as therapeutic targets in the treatment of AD. Recent studies indicate that stimulation of ET\textsubscript{B} receptors may provide neuroprotection. The purpose of this study was to determine the effect of selectively activating the ET\textsubscript{B} receptors following A\textbeta-induced cognitive impairment and oxidative stress in normal and diabetic rats.

**Methods**
Adult male Sprague-Dawley rats were treated with A\textbeta\textsubscript{1-40} (20 µg in 3 equally divided doses) in the lateral cerebral ventricles using sterotaxically implanted cannulas. A\textbeta was administered on day 1, 7 and 14 and all experiments were performed on day 15. The rats were treated chronically with ET\textsubscript{B} receptor agonist (IRL-1620) or antagonist (BQ788) for 14 days. Oxidative stress markers assessed were malondialdehyde (MDA), glutathione (GSH) and superoxide dismutase (SOD). Learning and memory behavior was assessed using the Morris water maze.

**Results**
A\textbeta treatment in normal and diabetic rats produced a significant (p<0.0001) increase in malondialdehyde (MDA) levels (516.13 ± 14.02 and 531.58 ± 10.21 nmol/g wet tissue, respectively) compared to sham group (112.1 ± 1.82 and 114.31 ± 2.05 nmol/g wet tissue, respectively). Antioxidants (superoxide dismutase and reduced glutathione) decreased following A\textbeta treatment compared to sham group. Treatment with IRL-1620 reversed these effects, indicating that ET\textsubscript{B} receptor activation reduces oxidative stress injury following A\textbeta treatment. Animals pretreated with BQ788 showed similar oxidative stress damage compared to vehicle group. In Morris swim task, A\textbeta treated rats showed a significant impairment in spatial memory. Rats treated with ET\textsubscript{B} receptor agonist, IRL-1620, significantly reduced the cognitive impairment induced by A\textbeta. However, blockade of ET\textsubscript{B} receptors by BQ788 followed by either vehicle or IRL-1620 treatment resulted in cognitive impairment similar to those of rats treated with vehicle alone. BQ788 blocked IRL-1620 induced improvement in cognition and oxidative damage.

**Conclusion**
The present study demonstrates that IRL-1620 administration prevents cognitive impairment and oxidative stress induced by A\textbeta suggesting that ET\textsubscript{B} receptor stimulation may be useful in the treatment of Alzheimer’s disease.