ET_B receptor agonist, IRL-1620 prevents beta amyloid (Aβ) induced cognitive impairment in normal and diabetic rats

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Background: Alzheimer's disease (AD) is a progressive brain disorder leading to impairment of learning and memory. Incidence of AD is higher in diabetic patients. Studies indicate that stimulation of ET_B receptors may provide neuroprotection. The present study was conducted to investigate the involvement of ET_B receptors in Aβ-induced cognitive impairment in non-diabetic and diabetic rats.

Methods: The expression of ET_B receptors was studied using Western blotting. Parameters of oxidative stress assessed were malondialdehyde (MDA), glutathione (GSH) and superoxide dismutase (SOD). Learning and memory behaviour was assessed using the Morris water maze. Rats divided into two groups (diabetic and non-diabetic) and were treated with Aβ(1-40) (20 µg, icv in 3 equally divided doses). Aβ was administered on day 1, 7 and 14 and all experiments were performed on day 15. In the diabetic group, streptozotocin (45 mg/kg, ip) was administered 3 days prior to Aβ injection. Rats were treated chronically with ET_B receptor agonist (IRL-1620) and antagonist (BQ-788) for 14 days. One-way analysis of variance followed by Bonferroni's post-hoc test was used for intergroup comparison with $P<0.05$ considered significant.

Results: Diabetic rats showed sluggish behaviour and decreased locomotion compared to non-diabetic rats. However, no difference was observed in cognitive impairment or oxidative stress parameters following Aβ treatment in non-diabetic and diabetic rats. Aβ treatment produced no change in ET_B receptor expression in the brain, and ET_B receptor expression was not altered by IRL-1620 or BQ-788 treatment. However, a significant increase in oxidative stress parameters as shown by an increase in levels of MDA and a concurrent decrease in GSH and SOD levels was observed following Aβ treatment in non-diabetic and diabetic rats. IRL-1620 produced a significant ($P<0.001$) decrease (278.4±8.5 nmol/g wet tissue) in MDA level compared to the vehicle group (516.1±14 nmol/g wet tissue) and reversed the decrease in GSH and SOD levels following Aβ treatment in non-diabetic and diabetic rats. In Morris water maze task, Aβ treated rats showed a significant ($P<0.0001$) impairment in spatial memory. Administration of IRL-1620 to Aβ treated rats produced a significant improvement in learning and memory compared to the vehicle group in both diabetic and non-diabetic rats. Changes induced by IRL-1620 were completely blocked by BQ-788.

Conclusion: Aβ treatment produced significant increase in oxidative stress parameters and loss of learning and memory, which was improved by ET_B agonist, IRL-1620.