Abstract

Obesity, a global health concern, is increasingly linked not only to metabolic disorders but also to cognitive impairments, including deficits in memory, learning, and executive function. Diet-induced obesity (DIO) has been shown to adversely affect hippocampal plasticity through mechanisms involving oxidative stress, neuroinflammation, and impaired neuronal signaling. As the hippocampus is essential for acquiring knowledge and retaining special information, therapeutic strategies targeting hippocampal dysfunction are essential for addressing obesity-associated cognitive decline.

Recent attention has shifted toward plant-derived phenolic compounds for their multi-targeted neuroprotective effects and favorable safety profiles. In this context, the naturally occurring phenolic component syringic acid (SA), which is found in various fruits, vegetables, and medicinal plants, has been shown to possess neuroprotective, anti-inflammatory, and antioxidative properties. The purpose of this study was to investigate how SA can enhance memory and learning in a diet-induced obesity-associated mouse model, with a focus on its impact on neuronal plasticity and behavior. We hypothesized that SA would enhance spatial memory and cognitive flexibility in diet-induced obese mice by upregulating synaptic markers such as PSD95 and NR2A, as well as plasticity-related proteins and transcription factors involved in memory formation, including cAMP response element-binding protein (CREB).

The study was conducted in both *in vitro* and *in vivo* systems. For the *in vitro* study, N2a neuronal cells were treated with different concentrations of SA (100, 200, 300, and 500 µM), and the status of calcium influx, memory consolidation, and plasticity-related molecules was then observed. In cultured N2a neuronal cells, SA upregulated the expression of plasticity-associated proteins, including NR2A, and PSD95, and facilitated calcium influx through NMDA and AMPA receptors. Mechanistic investigations revealed that SA activates CREB via a PKA-dependent pathway, leading to the enhanced expression of synaptic plasticity markers. The *in vitro* study demonstrated CREB activation and upregulation of plasticity-related proteins, which were significantly restored following SA treatment. Furthermore, PPARα was identified as a critical factor in reducing inflammation, as well as an upstream regulator of CREB activation. These findings highlight the potential of SA to promote synaptic plasticity and improve cognitive function through the PPARα-PKA-CREB signaling axis, offering promising insights into novel therapeutic strategies for cognitive impairments via the upliftment of neuronal plasticity.

The *in vivo* study was conducted by feeding male C57BL6 mice a high-fat diet (HFD) for 12 weeks in order to induce obesity and cognitive impairment. Mice in the treatment group were given oral SA (50mg/Kg of body weight) from week 8^{th} to week 12^{th}. Behavioral assessments were conducted using the Barnes maze and T-maze test, a validated paradigm to evaluate spatial learning, memory consolidation, decision-making, and goal-directed navigation. The performance of SA-treated DIO mice was compared with untreated DIO controls. Our behavioral data revealed that SA-treated mice exhibited significantly enhanced memory performance. They showed reduced latency to locate the escape area, indicating faster spatial learning and improved memory retrieval. Additionally, the SA group had many fewer reference and working memory errors, which may indicate better short-term retention and longer-term memory consolidation. Analysis of decision-making strategies revealed that SA-treated mice made fewer negative turns and more accurate choices, highlighting improved cognitive flexibility and reduced perseverative behavior. These behavioral changes were accompanied by reduced trial durations and more effective utilization of spatial cues, pointing to restored hippocampal-dependent navigation. At the molecular level, SA therapy increased the expression of phosphorylated CREB (p-CREB), a transcription factor that is essential for memory consolidation. Furthermore, in the brain, SA increased the expression of important synaptic plasticity-related proteins such as NR2A and PSD-95. These proteins are central to synaptic strength, plasticity, and neurotransmission, and their restoration further supports the observed behavioral improvements.

The modulation of these plasticity-related molecules suggests that SA may enhance synaptic remodeling and neuronal connectivity, which are typically compromised in DIO mice. These findings collectively demonstrate that SA effectively reverses obesity-induced cognitive impairments by enhancing neuronal plasticity and memory-related behaviors. The combined behavioral and molecular outcomes underscore SA's potential as a natural therapeutic agent capable of restoring cognitive function in metabolic disease conditions. Unlike many phytochemicals that show efficacy only *in vitro*, SA displayed significant *in vivo* activity, highlighting its translational relevance.

In conclusion, our study establishes SA as a promising compound for mitigating obesity-associated cognitive deficits. Through its ability to improve hippocampal function, reduce memory errors, and upregulate plasticity-associated signaling molecules, SA offers a multi-faceted approach to neuroprotection. These results pave the way for future investigations into the long-term cognitive benefits of SA and its possible integration into dietary or pharmacological interventions aimed at combating metabolic and neurodegenerative disorders.

Keywords: Syringic acid, diet-induced obesity, hippocampal plasticity, memory consolidation, spatial learning, CREB, synaptic proteins, cognitive flexibility.