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Quercetin Enhances Short-term Depression (STD) *via* Inhibiting Endocytosis

Quercetin, a natural flavonol compound found in traditional Chinese medicine, fruits, vegetables, and medicinal plants, has been the subject of numerous studies due to its potential therapeutic value[1]. Accumulated studies have demonstrated that quercetin can modulate neuronal excitability *via* different underlying mechanisms in the central nervous system[2-3]. However, the specific effects and mechanisms of quercetin in the central nervous system are still controversial, especially in the field of basic synaptic transmission.

The calyx of Held synapse displays classic features of conventional synapse, such as the presence of calcium, sodium, and potassium ion channels in the presynaptic nerve terminals, the ability to generate action potentials, and short-term synaptic plasticity[4-5]. Li *et al*. (Prog Biochem Biophys, 2023, **50**(6): 1391-1402. DOI: 10.16476/j. pibb. 2023.0191) investigated the presynaptic effect of quercetin using capacitance measurement techniques at the giant glutamatergic central synapse, the calyx of Held, which provides a unique feasibility to study the presynaptic kinetics of synaptic transmission. The authors showed that quercetin inhibits presynaptic vesicle endocytosis without affecting calcium influx and exocytosis. The slowdown of endocytosis further leads to inhibition of vesicle mobilization and the replenishment of the readily releasable pool (RRP). In addition, the quercetin-induced inhibition of vesicle endocytosis and RRP replenishment enhances the short-term depression (STD) during high-frequency repetitive stimulation.

This study provides new insights into the quercetin-modulated presynaptic mechanisms at the synapse of the calyx of Held and suggests a protective effect that prevents excessive excitatory synaptic transmission in brain circuits. On the other hand, the specific roles of quercetin in different brain regions (*e.g.*, cortex, hippocampus) remain to be explored in combination with the whole neural circuit. Finally, extensive basic research is required to confirm the exact treatment and the mechanism of quercetin in clinical diseases.

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