Effects of Rottlerin and MK-801 on Three Stages of Aversive Memory: Differential Involvement of Hippocampus

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SUMMARY

Rottlerin is a multifunctional drug used to treat cancer cells in the preclinical trials. It inhibits eukaryotic elongation factor 2 kinase (eEF2K) and increases the brain-derived neurotrophic factor (BDNF) protein levels in the hippocampus. The eEF2K, which phosphorylates eukaryotic elongation factor 2 (eEF2), is one of the downstream signaling molecules of the N-methyl-D-aspartic acid receptor (NMDAR). Moreover, rottlerin is a mitochondria-specific uncoupler that affects many protein kinases, such as PKC, Akt/PKB, and extracellular-signal-related kinases 1/2 (ERK1/2). Rottlerin, an eEF2K inhibitor, has recently been found to exert a fast-acting antidepressant-like behavior via increase of BDNF protein in the mouse hippocampus. Likewise, MK-801, a non-competitive antagonist of NMDAR, exerts a antidepressant-like effect similar to that of rottlerin. Both the NMDA receptor and PKC have long been implicated in the normal function of learning and memory. Furthermore, the NMDA receptor in the dorsal hippocampus is involved in long-term memory formation of the inhibitory avoidance task.

The inhibitory avoidance task is a one-trial learning task used to assess aversive learning and memory. It is also widely used in the preclinical research to measure avoidance/aversive behavior, which is one of the symptom clusters in the posttraumatic stress disorder (PTSD). We sought to examine the effect of two antidepressants, rottlerin and MK801, on memory acquisition, consolidation/reconsolidation, and retrieval of the inhibitory avoidance task. Since both rottlerin and MK801 increase BDNF protein in the hippocampus, which plays an essential role in enhancing long-term memory, we next examined whether the effects of rottlerin and MK-801 on inhibitory avoidance memory is via changes in the levels of BDNF and other related proteins in the hippocampus.

Our results indicate that systemic rottlerin impaired memory acquisition, consolidation and retrieval of the inhibitory avoidance memory, while had no effect on memory reconsolidation. Systemic MK-801 impaired acquisition of the same aversive memory, however, this impairment was caused by increase of shock sensitivity under the drug effect of MK-801. Intriguingly, MK-801 facilitated memory consolidation and retrieval of the inhibitory avoidance memory. Moreover, the intra-hippocampal infusion of rottlerin significantly impaired memory acquisition, consolidation and retrieval of the same aversive memory, indicating the effect of rottlerin is mediated by certain molecular players in the hippocampus. The different effects of rottlerin and MK-801 on inhibitory avoidance memory may involve distinct downstream signaling molecules, which is currently under intense investigation.

1) Experimental procedures

2) Systemic rottlerin impaired acquisition, consolidation, and retrieval of aversive memory, but did not affect reconsolidation of the same memory

3) Systemic MK-801 impaired acquisition, while facilitated consolidation, and retrieval of aversive memory. However, MK-801 did not affect memory reconsolidation

4) Systemic MK801 increased shock sensitivity, whereas rottlerin did not change it. MK-801 modulated memory differently depending on shock intensities

5) Intra-HIPP infusion of rottlerin impaired memory acquisition, consolidation of IA memory, but did not affect its reconsolidation and retrieval

6) Intra-HIPP infusion of MK-801 facilitated consolidation and retrieval of IA memory, but did not affect its acquisition and reconsolidation

7) Histology