One feature of long-term memory is that it requires the synthesis of new RNA and proteins. The marine snail Aplysia has been used for the study of learning and memory from molecular to behavioral aspects. Although there have been many attempts to identify long-term memory-related genes in Aplysia, the number of cloned memory-related genes is still limited. In this study, to provide genetic information on Aplysia in a large scale, several cDNA libraries were constructed from nervous system of Aplysia kurodai and 11755 expressed sequence tags (ESTs) were collected. Of those ESTs, 3765 clones were singletons and the others were assembled into 1094 contigs, representing total 4859 putative transcripts. The putative genes were functionally classified using the Gene Ontology (GO) system which describes how gene products behave in a cellular context and synaptic transmission and plasticity-related genes were revealed based on the BLASTX algorithm. These analyses showed that many structural and signaling molecules were represented. cDNA microarrays were constructed with around 7000 ESTs and used to screen the differentially expressed genes by 5-hydroxytryptamine (5-HT)-treatment which produces long-term facilitation and sensitization. The up- or down-regulation of selected clones were confirmed by performing RT-PCR analysis. The functional study of those genes which are good candidates for memory-related genes will provide insights into the understanding of molecular mechanisms of learning and memory.

The mechanisms of transcriptional regulation of memory consolidation have been extensively studied in diverse nervous systems such as rodent hippocampus and Aplysia sensory-to-motor synapse. However, the post-transcriptional regulation of memory consolidation is relatively less investigated. Using cDNA microarray, a gene that is gradually induced in response to 5-HT stimulation which produces long-term facilitation of Aplysia synapses was cloned. This gene was characterized as an AU-rich element (ARE) binding protein, namely, ApAUF1. Cloned ApAUF1 acts as a destabilizing factor for the transcription factor ApC/EBP. Moreover, ApAUF1 overexpression inhibited the induction of ApC/EBP mRNA and long-term facilitation by repetitive 5-HT treatment. These experiments suggested that cloned ApAUF1 is a novel negative regulator that can balance the positive factors involved in long-term facilitation. These data also indicate that the post-transcriptional modification of mRNA plays a critical role during memory consolidation.

Finally, the role of NMDA NR2B subtype receptor in prefrontal cortex of adult mouse in fear conditioning was investigated. Pharmacological or genetic blockade of NR2B in prefrontal cortex impaired the formation of early fear memory. Moreover, the inhibition of hippocampal NR2B did not block the fear conditioning. These results demonstrated that the NR2B subunit of NMDA receptor in the prefrontal cortex is critically involved in contextual memory.

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