cAMP-induced Aβ production and its role in the expression of LTP

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Cyclic adenosine monophosphate (cAMP) is essential for the expression of LTP, the electrophysiological substrate of learning and memory[1]. Many studies have shown that pharmacological and genetic manipulations of the cAMP/PKA/CREB pathway influence hippocampal late LTP and long-term memory[2,3].Specifically, inhibition of PDE4-mediated cAMP breakdown enhances LTP and improves memory[4,5].

Recent data indicate that amyloid beta 42 ($A\beta_{42}$), besides playing a pathogenic role in Alzheimer's disease, also exerts physiological functions in the brain.Indeed, picomolar concentrations of $A\beta_{42}$, normally produced in the brain, potentiate hippocampal LTP and improve memory, while $A\beta_{42}$depletion does the opposite[6,7].

Since LTP is dependent on both cAMP and $A\beta_{42}$, we investigated the neurochemical relationships between these two signaling molecules.

Our results show that increasing cAMP in mouse N2a cells, stably expressing WT human APP695, with rolipram (ROL 0.1–10 μM), 8Br-cAMP (1 μM-1mM) or forskolin (FSK 1μM-10μM) caused the enhancement of APP and $A\beta_{42}$ levels. The same results were obtained with 6-MB-cAMP (1-100 μM) but not with 8-pCPT-2-O-Me-cAMP-AM (0.01-25 μM), indicating that the cAMPeffects were mediated by PKA but not by EPAC. Moreover, we also found that the increaseof APP and $A\beta_{42}$ induced by 1 μM FSK or by the PKA activator 6-MB-cAMP (100μM) was blocked by the protein synthesis inhibitor cycloheximide (80 μg/ml), but not by the transcription inhibitor actinomycin D (4 mg/ml); accordingly, no changes of APP mRNA were detected in response to FSK or to 6-MB-cAMP.

The effects of cAMP could be reproduced in the hippocampus as treatment of rat hippocampal slices with ROL(100 μM), FSK(100 μM) or 6-MB-cAMP (100 μM) resulted in a significant increase of APP and $A\beta_{42}$levels.

In order to understand the downstream mechanisms involved in the cAMP-mediated, PKA-dependent regulation of APP synthesis and $A\beta_{42}$production, we studied whether hnRNP-C and FMRP, two RNA binding proteins involved in APP expression, could be the cAMP effectors.Using RNA immunoprecipation and silencing techniques, we found that neither hnRNP-C nor FMRP are necessary for cAMP to stimulate APP translation. In fact,FSK-induced cAMP accumulation was not associated with an increase of APP mRNAin the hnRNP-C immunocomplex, and hnRNP-C or FMRP knocking down did not alter the APP/Aβ response to FSK. Furthermore, the effects of FSK were not affected by blocking the PKA-activated PPA2, which has been demonstrated to provoke FMRP degradation. In future studies, we will investigate the role of other factors that are involved in the post transcriptional regulation of APP mRNA, such as nucleolin[8], RCK/p54[9], IRP1[10], and miRNA[11].

Finally, we investigated the functional relationships between cAMP and Aβ in LTP.In WT mice, a weak tetanic stimulation of the Schaffer collateral pathway elicited LTP in CA1 neurons that was reinforced by perfusion of hippocampal slices with 100 nM ROL for 20 min before stimulation. On the contrary, the effect of ROL was absent in slices obtained from APP KO mice or in slices obtained from WT animals and treated with anti-Aβ antibodies (JRF/rAb2, 4 μg/ml; M3.2, 4 μg/ml).

Our data demonstrate that the second messenger cAMP controls APP expression and revealed a novel cAMP/PKA/APP/Aβ pathway that plays a key role in the expression of LTP.

References

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