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A study upon short term and long term memory mechanisms

D Lana, F Cerbai, MG Giovannini. *University of Florence, Department of Preclinical and Clinical Pharmacology, 50139, Italy*

Memory can be subdivided in short term and long term memory. Short term memory can be established by covalent modifications of pre-existing proteins while long term memory requires protein synthesis, in particular in the synaptodendritic compartment. The mammalian target of rapamycin (mTOR) regulates protein translation and thus cell growth, proliferation, survival and synaptic plasticity. Here we examined the effect of rapamycin (RAPA) and scopolamine on short and long term memory using a step-down inhibitory avoidance task, performing recall 1, 4 and 24 h after acquisition in adult Wistar rats (250 g). Number of animals ranged between 6 and 10. An icv cannula was inserted under general anesthesia with chloral hydrate. RAPA (3 nml/10 µl) was injected icv 30 min before acquisition trial. This time was chosen on the basis of RAPA diffusion kinetics obtained using MALDI-TOF-TOF showing that RAPA diffused to the hippocampus within 20-40 min after icv injection. Acquisition (AL) and recall (RL) latencies to step down the platform were measured. AL were not different between vehicle and RAPA treated rats. Animals treated with vehicle acquired the behaviour, as shown by RL that was significantly longer than AL at 1 and 4 h (short term memory) and 24 h (long term memory) after acquisition. A significant increase of mTOR activation was present in CA1 pyramidal neurons at 1 h (+95%; $P<0.01$) and 4 h (+114%; $P<0.001$) but not at 24 h (+28%, ns) after acquisition. RAPA did not affect short term memory 1 and 4 h after acquisition (RL: controls: 297.3±2 sec; RAPA treated rats at 1 h 243± 8, at 4 h 240±33 sec; n.s.). RAPA impaired long term memory at 24 h after acquisition (RAPA treated rats: 182±34 sec, $P<0.05$ vs controls). RAPA significantly inhibited mTOR activation in CA1 pyramidal neurons. Statistical analysis (two-way ANOVA) showed that RAPA significantly modified mTOR activation in CA1 (Treatment: $F_{1,21}=7.62$, $P<0.05$; Time: $F_{3,21}=8.87$, $P<0.001$; TreatmentxTime: $F_{3,21}=10.46$, $P<0.001$) at 4 h after acquisition. A significant increase of p70S6K activation was present in CA1 neurons at 4 and 24 h after acquisition. RAPA treatment significantly inhibited p70S6K activation. Statistical analysis (two-way ANOVA) showed that RAPA significantly modified p70S6K activation in CA1 (Treatment: $F_{1,23}=29.49$, $P<0.01$; Time: $F_{3,23}=59.93$, $P<0.05$; TreatmentxTime: $F_{3,78}=4.99$, $P<0.05$) at 24 h after acquisition. The non selective muscarinic antagonist scopolamine (1.5 mg/kg, ip) administered 30 min before acquisition imparied short term but not long term memory encoding (Treatment: $F_{1,59}=13.54$, $P<0,0001$; Time: $F_{3,59}=59.60$, $P<0,0001$; TreatmentxTime: $F_{3,59}=11.47$, $P<0.0001$). Statistical analysis (two-way ANOVA) showed that scopolamine increased mTOR activation in CA1 1 h after acquisition (Treatment: $F_{1,33}=10.37$, $P<0,001$; Time: $F_{3,33}=59.19$, $P<0,0001$; TreatmentxTime: $F_{3,33}=7.15$, $P<0.05$). Our data demonstrate that mTOR and p70S6K activation are responsible for long term memory formation in the hippocampus. These results support the idea that the cholinergic system is involved in short term but not long term memory encoding. Taken together these date give strenght to the hypothesis that distinct molecular mechanisms are at the basis of the two different forms of memory.