

cGMP MODULATES LONG-TERM POTENTIATION AND MEMORY BY ENHANCING ABETA PRODUCTION

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It is well known that cyclic guanosine monophosphate (cGMP) is involved in the regulation of long-term potentiation (LTP), a synaptic plasticity phenomenon that is generally considered the electrophysiological substrate of learning and memory formation. As a matter of fact, a large body of evidence has shown that inhibition of phosphodiesterase(PDE)-mediated degradation of cGMP enhances LTP and ameliorates memory in healthy and diseased brains¹. Interestingly, in the last decade it has been consistently demonstrated that, contrary to its deleterious effects in Alzheimer's disease, the amyloid-beta (A β) peptide is necessary at low physiological concentrations for LTP expression and cognitive processes²⁻⁴.

Therefore, in the present study we investigated whether cGMP and A β could functionally interact to trigger LTP and, therefore, memory formation.

First, we investigated if cGMP could influence A β ₄₂ production in cultured neuronal cells (N2a). Indeed, blockade of the cGMP-metabolizing enzyme PDE5 with sildenafil or vardenafil (100 μ M) increased intracellular cGMP in N2a cells by 5 and 23 folds, respectively, and this effect was paralleled by a 50 to 100% enhancement of A β ₄₂ levels. Pearson's correlation coefficient between PDE5 inhibitor-induced cGMP and A β ₄₂ production was 0.97, indicating a very strong relationship between the two events. This view was confirmed by the observation that the sildenafil/vardenafil-induced increase of A β ₄₂ was significantly reduced when cGMP synthesis was inhibited by the selective soluble guanylyl cyclase blocker ODQ (50 μ M). Of note, sildenafil and vardenafil (100 μ M) were able to increase A β ₄₂ production also in slices of rat hippocampus, a brain region with a key role in learning and memory.

Analyzing the amyloidogenic pathway, we found that, both in N2a cells and hippocampal slices, the vardenafil-induced enhancement of A β ₄₂ production occurred in the absence of changes in APP expression. Apparently, vardenafil did not affect also the activity of BACE-1, the APP-cleaving enzyme that is necessary for A β ₄₂ formation. However, using the OptiCAB assay (Optical Convergence of APP and BACE-1)⁶, we observed that vardenafil treatment was able to significantly increase the approximation of APP and BACE-1 and their co-localization into the endo-lysosomal compartment of cultured hippocampal neurons, a cellular district where APP cleavage preferably occurs.

As for hippocampal LTP, we confirmed that vardenafil (10 μ M) was able to convert early LTP into late LTP. However, this effect of the PDE5 inhibitor was not observed when hippocampal slices were pretreated with an anti-A β antibody (M3.2 mAb; 2 μ g/ml) for 20 minutes before the tetanus, but it was rescued by the addition of human A β ₄₂ (200 pM). In addition, the LTP potentiating effect of vardenafil was absent in hippocampal slices obtained from APP knock out mice.

Finally, Vardenafil (1 mg/kg) was able to enhance wild type mice memory in the object location task, whereas it was ineffective in APP knock out mice.

In conclusion, we have discovered a new functional relationship between cGMP and A β , which is necessary for LTP and memory to work in physiological conditions. These findings could represent the mechanism of action of PDE5 inhibitors that might exert their cognitive-enhancing effects via a positive modulation of A β in the healthy brain. Moreover, our data highlight the importance of fully understanding the physiological role(s) of A β to design effective and safe AD therapies, since A β lowering treatments could worsen memory instead of ameliorating it.

References

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